POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

TITLE: A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study

COMPOUND: Valproate and other antiepileptic drugs

STUDY NUMBER: VALNAC09345 (Sanofi internal reference)

Amended Version of the Study Protocol 02 October 2023 **Total number of pages** 287

PASS INFORMATION

TITLE	A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study
PROTOCOL VERSION IDENTIFIER	Version 7.0
DATE OF LAST VERSION OF PROTOCOL	23 January 2023
EU PAS REGISTER NUMBER	EUPAS34201
ACTIVE SUBSTANCE	Antiepileptic drugs (AEDs) including valproate ATC WHO code: N03A
MEDICINAL PRODUCT(S)	Antiepileptic drugs (AEDs) including valproate
PRODUCT REFERENCE	Information is detailed in the cover letter's Annex 1
PROCEDURE NUMBER	EMEA/H/A-31/1454
MARKETING AUTHORISATION HOLDER(S) (MAH)	The joint initiative involves several companies via a consortium APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN; VIATRIS SANTE (LYON): FR; VIATRIS GX BV/SRL: BE; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; SANOFI R&D; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE; WOCKHARDT UK LIMITED
JOINT PASS	YES
RESEARCH QUESTION AND OBJECTIVES	**Overall aim** The aim of this retrospective cohort study is to examine the association between paternal exposure to valproate at conception and the risk of NDD, including autism spectrum disorders (ASD), as well as congenital malformations (CM) in offspring. Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam. **Primary objective** 1. Investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared

	to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception. **Secondary objectives** 2. Investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception, in Norway and Denmark. 3. Describe AED exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort. 4. Identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine or levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers. **Exploratory objectives** 5. To describe the putative risk factors and frequency of NDD, including ASD, as well as CM in offspring paternally exposed to valproate (in combination with other AEDs) and to other AEDs (in combination with other AEDs, excluding valproate) at the time of conception. 6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception. 7. To investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception in Sweden. 8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.
COUNTRY(-IES) OF STUDY	The study will be conducted in Denmark, Sweden, and Norway
AUTHOR	Ana Cristina Santos, PhD, MPH Florent Richy, PhD, MPH On behalf of IQVIA and the Consortium

MARKETING AUTHORISATION HOLDER'S

MARKETING AUTHORISATION HOLDER(S)	This section provides contact details of the companies involved in the consortium APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN; VIATRIS SANTE (LYON): FR; VIATRIS GX BV/SRL: BE; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; SANOFI R&D; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE; WOCKHARDT UK LIMITED
MAH CONTACT PERSON (on behalf of MAHs)	Amélie Prieur, Deputy QPPV SANOFI R&D Avenue Pierre Brossolette 91385 Chilly Mazarin France mailto: amelie.prieur@sanofi.com

This protocol contains confidential information that should only be disclosed first to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

1. TABLE OF CONTENTS

1.1 LIST OF FIGURES

1.2 LIST OF TABLES

2. LIST OF ABBREVIATIONS

Abbrevation	Definition
ADHD	Attention-Deficit/Hyperactivity Disorder
AED	Anti-Epileptic Drug
ARND	Alcohol-Related NDD
ASD	Autism Spectrum Disorder
ATC	Anatomical Therapeutic Chemical
CHD	Congenital Heart Defects
CI	Confidence Interval
CM	Congenital Malformations
CoE	Centre of Excellence
CPR	Danish Civil Registration System
DDD	Defined Daily Dose (classification by WHO)
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	Ethics Review Board
EU	European Union
FAS	Foetal Alcohol Syndrome
GVP	Good Pharmacovigilance Practices
HR	Hazards Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
ICH	International Conference on Harmonisation
IQ	Intelligence Quotient
IQR	InterQuartile Range
ISPE	International Society for Pharmacoepidemiology
IVF	In Vitro Fertilisation
LMP2	Last Menstrual Period + 2 weeks
MAH	Marketing Authorisation Holders
NDD	Neurodevelopmental disorders
NEMEA	Northern Europe, Middle East and Africa
NTD	Neural Tube Defects
OR	Odds Ratio
PAE	Prenatal Alcohol Exposure
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PH	Proportional Hazard
PI	Principal Investigator
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity-Score
RWI	Real-World Insight
SAP	Statistical Analysis Plan
SD	Standard Deviation
SES	Socioeconomic Status
SOP	Standard Operating Procedures
SSRIs	Selective Serotonin Reuptake Inhibitors
TS/CT	Tourette Syndrome and Chronic Tic Disorder
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Responsible Party	Name and Affiliation
Consortium	Valproate consortium of MAH (contact details for all MAHs are provided in Annex 4. Marketing Authorisation Holders (MAHs) Details)
Sponsors	All MAHs involved in the valproate consortium
MAH responsible for submissions to HA	SANOFI
Contracting vendor	**IQVIA LTD,** a company registered under the laws of England and Wales, company registration number 03022416 Address: The Point, 37 North Wharf Road, Paddington, W2 1AF, United Kingdom Phone: +44 2030574423 Contact: Richy Florent
Principal Investigator	Florent Richy, PhD, MPH (Principal Investigator), Director of Epidemiology, Real-World Solutions
IQVIA project team	• Florent Richy, PhD, MPH (Principal Investigator), Director of Epidemiology • Project Manager: Vanessa Marzola, MSc • Epidemiological Oversight: Ana Cristina Santos, PhD, MPH • Biostatistical Oversight: Alessandra Venerus, MSc
Medical and Methods Advisor	Ian Wong, PhD Marte Bjork, PhD, MD

IQVIA is member of the European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP).

4. ABSTRACT

Full Study Title

A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study

Rationale and background:

Valproate-containing medicines are approved nationally in the European Union for epilepsy and bipolar disorder, and in some countries, for the prevention of migraine. In recent years, due to an increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD), and congenital malformations (CM) in offspring after valproate exposure in utero, the use of valproate has been restricted to cases in which no other effective or tolerated treatment is available in women of childbearing potential or in pregnant women suffering from epilepsy; it has been contraindicated in pregnant women suffering from bipolar disorder.

There is currently no real-world evidence of an increased risk of CM and NDD including ASD in offspring following paternal exposure to antiepileptic drugs (AEDs). Therefore, and following the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation dated 08 February 2018, a post-authorisation safety study (PASS) is being conducted to evaluate the association between paternal exposure to valproate and risk of NDD, including ASD, as well as CM in offspring.

Overall aim

The aim of this retrospective cohort study is to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD, as well as CM in offspring. Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam.

Primary objective

1. Investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.

Secondary objectives

2. Investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception, in Norway and Denmark.
3. Describe AED exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort.
4. Identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine or levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers.

Exploratory objectives

5. To describe the putative risk factors and frequency of NDD, including ASD, as well as CM in offspring paternally exposed to valproate (in combination with other AEDs) and to other AEDs (in combination with other AEDs, excluding valproate) at the time of conception.

6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception.
7. Investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception in Sweden.
8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.

Study design

This study is a population-based retrospective cohort design using secondary data obtained from national registries. The outcomes of interest in the offspring are NDD including ASD (primary outcome), and a composite of CM (secondary outcome).
For the evaluation of NDD, including ASD, the population for analysis will be comprised of live births for whom medical record linkage to mother and father is available within such registries. For the evaluation of CM, the population for analysis will be comprised of live births, stillbirths and spontaneous abortions[1] during gestation (2nd and 3rd trimester) for whom medical record linkage to mother and father is available within such registries, for Norway and Denmark. For Sweden the corresponding population for analysis will be comprised of live births only. The primary outcome of interest is NDD, including ASD in offspring up to 12 years of age based on ICD-10 diagnostic codes, as recorded in the National Patient Registries. The secondary outcome of interest is a composite of CM diagnosed in offspring up to 12 years of age, stillbirths and spontaneous abortions-based on ICD-10 diagnostic codes, as recorded in the National Patient Registries and Medical Birth Registries. The primary exposure of interest is paternal use of valproate during the spermatogenic risk window prior to conception of the offspring (defined by the first day of the last menstrual period date plus two weeks [LMP2] of the mother within the linked family unit). Exposure information will be derived from prescription data, as recorded in the National Prescription Registries for each country (from 2005 in Sweden, 2008 in Norway and 1995 in Denmark) to 31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway. Country-specific cohorts of eligible linked family units will be identified. These cohorts will be combined (in terms of aggregated results) into an all-Nordic cohort (Sweden, Norway, Denmark for the primary outcome and Norway, Denmark for the secondary outcome) where feasible to further increase validity and statistical power.

Population:

Setting

Subjects for inclusion in the study will be selected from the national registries of Sweden, Denmark, and Norway. These are large, longitudinal patient-level registries that collect secondary data. The study population will comprise live births, stillbirths and spontaneous abortions for whom medical record linkage to mother and father is known within the registries.

In order to perform the data extraction, the following inclusion and exclusion criteria will be applied:

Inclusion criteria for data extraction

- Singleton pregnancies, with known pregnancy-length of at least 12 weeks within the study time period;
- Pregnancies linked to both mother and father within the study time period;

[1] Data about voluntary abortions, that can have a diagnosis of CM, are not linked to fathers in any of the countries at study.

- Father with a continuous enrolment in the database for ≥12 months prior to linked mother LMP2 date;
- Father with at least one AED in the data available.

For Sweden the inclusion criteria are slightly different, as only live births can be included:

- Singleton pregnancies resulting in live births;
- Pregnancies linked to both mother and father within the study time period;
- Father with a continuous enrolment in the database for ≥12 months prior to linked mother LMP2 date;
- Father with exposed to at least one AED during 192 days prior to 28 days after LMP2 date

Exclusion criterion for data extraction

- Adopted children;
- Pregnancy associated with in vitro fertilisation (IVF);
- Pregnancies with missing gestational age and/or missing maternal LMP2 (for these pregnancies it will not be possible to identify the exposure window for the study)

Two different cohorts will be constructed for analysis with further inclusion/exclusion criteria (see below) to address the research questions related to the primary (NDD including ASD), and secondary (CM) outcomes.

Additional inclusion criteria for the primary outcome (NDD including ASD)

- Singleton born alive within the study time period (i.e. the birth of only one child during a single delivery)
- Mother with a continuous enrolment for ≥12 months prior to child birthdate

Additional exclusion criteria for the primary outcome (NDD including ASD)

- Offspring whose parent(s) have a history of CM or NDD (according to available records)

Additional inclusion criteria for the secondary outcome (CM)

- Mother with a continuous enrolment of 12 months prior to index date (12th week of gestation in Norway, 22nd in Denmark, offspring birth date in Sweden)

Additional exclusion criteria for the secondary outcome (CM)

- Offspring whose parent(s) have a history of CM or NDD (according to available records)

Additional exclusion criteria will be applied for the comparative, exploratory and sensitivity analyses.

Variables*:*

Primary outcome

NDD including ASD, will be defined as a diagnosis of at least one the ICD-10 codes presented in codelist Table 10. Please note that ASD codelist is presented separately in the codelist Table 8, and NDD without ASD in the codelist Table 9.

Secondary outcome

CM will be evaluated as a composite endpoint among live births within 12 years after birth for Denmark and within 10 years after birth for Norway, spontaneous abortions (during the second or third trimester, Norway and Denmark only) and stillbirths (during the second or third trimester, Norway and Denmark only) as a diagnosis of at least one of the following ICD-10 codes defined as CM according to the EUROCAT categories Guide 14. CM will be defined as a diagnosis of at least one of the ICD-10 codes presented in codelist Table 11. Please note that major CM codelist is presented separately in Table 12 and minor CM codelist in Table 13.

Data Sources:

- The National Registries from Sweden, Norway and Demark

Study size:

For the primary outcome, assuming a risk of 4% of NDD, including ASD, in the reference group (offspring exposed paternally to lamotrigine/levetiracetam monotherapy), a sample size of 1178 offspring within-family linked units (589 per exposure group) would be needed to observe a HR of 2.0 (i.e. doubling of risk in offspring paternally exposed to valproate) with 5% significance and 80% power.

As the comparative evaluation of CM as a composite outcome will be secondary, sample size estimation does not apply. However, assuming a minimum effect size of 2.5 for major CM as reported in live and non-live births for Norway and Denmark, where the background incidence was 3%, with 80% power, a study with a total sample size of 826 family linked offspring (n=413) in the valproate monotherapy group and n=413 in the comparator monotherapy group would be desirable. With the assumption that major CM outcome is nested within the secondary composite outcome, the sample size should also be sufficient to observe the desired effect size for the comparative analysis of the composite secondary endpoint for Norway and Denmark only.

Data analysis:

- Two cohorts will be constructed to evaluate the effect of the paternal valproate exposure on primary and secondary outcomes.
- A STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) diagram will be provided to show cohort exclusions step by step.
- For descriptive analysis of NDD (including ASD), paternal characteristics at conception and maternal characteristics at delivery (index date) will be described overall and by paternal exposure group including demographic and other characteristics such as comorbidities and medication use.
- For descriptive analysis of CM, paternal characteristics at conception and maternal characteristics at the index date (country-specific) will be described overall and by paternal exposure group including demographic and other characteristics such as comorbidities and medication use.
- Demographic and health characteristics of offspring at index date (or during follow-up, as appropriate) will be provided separately for both cohorts, by paternal exposure groups.
- Distribution of the outcomes at study will be presented, separately for each cohort, by paternal exposure group.
- Paternal AED exposure and maternal AED exposure will be characterised by cluster analysis.
- For the primary outcome, a crude and a propensity-score-weighted Cox proportional hazards regression model will be fitted to estimate a hazard ratio (HR) (+ 95% CI) between offspring paternally exposed to valproate and offspring paternally exposed to lamotrigine/levetiracetam (reference group).
- For the primary outcome, the risk and time to onset of NDD will be described by the cumulative incidence (+ 95% CI) of incident events, and cumulative hazard rate (+ 95% CI) of incident events over time. These statistics will be presented for the overall cohort and separately for offspring paternally exposed to valproate or lamotrigine/ levetiracetam (composite and separately).
- For the secondary outcome (country-specific), a crude and a propensity-score-weighted logistic regression model will be fitted to estimate the odds ratio (OR) (+ 95% CI) of CM between

offspring paternally exposed to valproate and offspring paternally exposed to lamotrigine/levetiracetam.

- For the secondary outcome (country-specific), incidence proportion (+ 95% CI) will be calculated both for the composite CM endpoint and separately for specific CM target body system organ groups classified according to EUROCAT categorization (Norway and Denmark only). These statistics will be presented for the overall cohort and separately for offspring paternally exposed to valproate or lamotrigine/ levetiracetam (composite and separately).
- Assuming country-specific analyses have been completed, results for the primary outcome (all countries) and secondary outcome analyses (Norway and Denmark only) can also be combined using a meta-analysis approach.
    - Several sensitivity analyses will be conducted
        - Variation of exposure time window for primary outcome
        - Outcome of interest restricted to ASD specifically (ignoring all other NDD diagnoses)
        - Exclusion of offspring with a birth weight lower than 1000gr or born prior to 8th month of pregnancy, for primary outcome
        - Handling of missing diagnoses for CM outcome
        - Simple pairwise comparison valproate vs lamotrigine and valproate vs levetiracetam in monotherapy
        - Comparison of the PS-weighted model with the traditional covariate adjustment model
        - Effect of paternal exposure to valproate on NDD by inclusion of offspring exposed to AEDs after birth, and/or diagnosed with epilepsy
        - Validation of the assumption that individuals are exposed to one DDD per day
        - Narrow case definition for secondary outcome - focus on CM in live births
        - Continuous measure of cumulative exposure
        - Categorical measure of cumulative exposure
        - Narrow case definition for primary outcome
    - Descriptive analysis of missing data will be conducted

The populations at study will include each individual offspring (or non-live birth) as the unit for analysis, therefore if the mother and father have more than one offspring they can be included more than once in the study; each offspring/non-live birth will coincide with the linked triple offspring/non-live birth, mother and father. Furthermore all variables collected for fathers and mothers will be re-calculated for each pregnancy.

Milestones

- Study period allowing 24 months prior to index date: from January 1997 (Denmark), January 2010 (Norway) and 2007 (Sweden) to 31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway.
- Registration in the EU PAS register: Q1 2020, after endorsement of protocol and before data extraction.
- Anticipated start of data extraction: Q4 2020

- End of data extraction: Q1 2021
- Progress report(s): Estimated Q1 2021 (12 months after PRAC endorsement)
- Interim report(s): Estimate Q3 2021 (Country-specific)
- Final report of study results: 23 January 2023, in accordance with PRAC
- Final report of study results v1.1, second submission: 27 March 2023
- Addendum to the final report of study results v1.1 (report on sensitivity analysis 2 and exploratory analysis 8): 27 March 2023
- Annex to the final report of study results v1.1 (compilation of sensitivity analysis tables): 27 March 2023
- Request for Amendment received from PRAC: 05 May-13 June 2023
- Partial Responses to List of PRAC Questions: 10 July 2023
- Submission of the deliverables related to results of the Norwegian re-run analyses: due 23 October 2023
- Submission of updated protocol v7: due 23 October 2023

NB: Ethics and data request process in the countries of interest has been known to take more than 12 months in some cases. In anticipation of this, in the absence of data at the interim report due date(s), a progress report will be submitted. The final report submission date, therefore, will be driven largely by the date of data acquisition in each country of interest.

5. AMENDMENTS AND UPDATES

Number	Date	Section	Description of change made	Justification	Minor or Major Change
1	November 2022	Title	Switch the title from "including autism spectrum disorders" to "including autism spectrum disorder" (singular).	Editorial change	Minor
2	November 2022	PASS Information	MAH participating in Consortium.	Update of MAH list	Minor
3	November 2022	PASS Information	The following change was made to the sentence "Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam which are considered the first-line treatment." To "Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam which are considered a safer treatment."	Update according to the current evidence	Minor
4	November 2022	Document	Use of British English spelling or grammar.	Editorial change	Minor
5	November 2022	2	Abbreviation addition of FAS.	Editorial change	Minor
6	November 2022	3	Project team updates.	Change of internal IQVIA affiliation	Minor
7	November 2022	4	The following updates have been made to abstract based on corresponding changes in the main protocol: A sentence in the first paragraph was reworded to reflect the current evidence. Paternal exposure to lamotrigine or levetiracetam considered as safer treatment and references to support this sentence were added. Study period	Document consistency	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			Inclusion criteria for data extraction: Sweden Exclusion criteria: all countries Analysis: propensity-score weighting; definition of family unit. In sensitivity analyses: Outcome of interest restricted to ASD specifically (ignoring all other NDD diagnoses) and Narrow case definition for the primary outcome. Milestones dates were updated.		
8	November 2022	6	In the sentence starting with "Due to the long,.. final study report is planned for 23 January 2023 (where it was previously estimated Q3 2022)". In table 1, the planned date for the Final report of study results was changed to 23 January 2023. In the sentence, "An interim report will be submitted to the PRAC 6-months after, and the final report within 12 months thereafter" was changed to "…and the final report in the 23 January 2023, as in accordance with PRAC."	Change of the planned date for delivering the final report of the study results, as in accordance to PRAC	Minor
9	November 2022	7.1	The sentence starting with "In recent years… was reworded to better reflect the current evidence. The sentence starting with Choi et al. used in utero exposure to valproate should be	A more suitable reference was added	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			replaced with 'Previous literature found that paternal exposure to valproate in mice might lead to behavioural alterations in offspring (4)'. Note that the reference is also changed with Ibi D, Fujiki Y, Koide N, Nakasai G, Takaba R, Hiramatsu M. Paternal valproic acid exposure in mice triggers behavioral alterations in offspring. Neurotoxicol Teratol. 2019 Dec;76:106837. In the sentence starting with “Large population-based studies…” the word “countries” was replaced by “databases”.		
10	November 2022	7.2	There is currently no real-world evidence of an increased risk of NDD including ASD, and CM in offspring following paternal exposure to antiepileptic drugs (AEDs), rephrased as “There is currently scarce real-world evidence of an increased risk of NDD including ASD, or CM in offspring following paternal exposure to antiepileptic drugs (AEDs) ”.	Editorial change	Minor
11	November 2022	8	The following change was made to the sentence “Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam which are considered the first-line treatment.” To “Paternal exposure to valproate will be compared to paternal	Update according to the current evidence	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			exposure to lamotrigine or levetiracetam which are considered a safer treatment." References were added to support this change.		
12	November 2022	9.1	Footnote 2: "Data about voluntary abortions, that can have a diagnosis of CM, are not linked to fathers in none of the countries at study". Rephrased to: "Data about voluntary or medically required abortions, that can have a diagnosis of CM, are not linked to fathers in none of the countries at study".	Editorial change	Minor
13	November 2022	9.1	Calendar end date was removed from Figure 1 and 2, and a more detailed information regarding the study period was added to section 9.3.2.1.	Editorial change	Minor
14	November 2022	9.1 - 9.2.1 - 9.3.2.1	"The study time period will end in December 2017 (or last available date) for all countries" rephrased to "The study time period ends on 31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway".	Extended the study time period	Minor
15	November 2022	9.2.2	Added "Note: For Sweden the inclusion criteria are slightly different, as only live births can be included: • Singleton[4] pregnancies resulting in live births; • Pregnancies linked to both mother and father within the study time period; • Father with a continuous enrolment in	Specification of the inclusion criteria for Sweden since only live births can be included in the cohort	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			the database for ≥12 months prior to linked mother LMP2 date; • Father with at least one exposure to AED during 192 days prior to 28 days after LMP2 date".		
16	November 2022	9.2.2	Additional operational exclusion criteria added: Pregnancies with missing gestational age and/or missing maternal LMP2 (for these pregnancies it will not be possible to identify the exposure window for the study).	An additional exclusion criteria will be applied during the extraction phase to assist with operationalisation of the analyses (although this will not be considered part of the study's eligibility criteria)	Minor
17	November 2022	9.2.3.1 and 9.2.3.2	The study time period was removed from Figure 3, Figure 4a and Figure 4b, and a more detailed information regarding the study period was added in section 9.3.2.2 Figure 4a and 4b, were renamed to figure 4 and figure 5, respectively.	Extended the study time period	Minor
18	November 2022	9.3.1	The sentence "As reported in section 9.7.3.2, in the primary analysis, paternal exposure to valproate (monotherapy) will be compared to paternal exposure to lamotrigine or levetiracetam (composite monotherapy) which are considered a first-line treatment" was changed to "As reported in section 9.7.3.2, in the primary analysis, paternal exposure to valproate (monotherapy) will be compared to paternal exposure to lamotrigine	Document consistency	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			or levetiracetam (composite monotherapy) which are considered a safer treatment" Figures 5 and 6 were updated to Figures 6 and 7, respectively.		
19	November 2022	9.3.1.1	Two of the exposure periods are considered fixed and two not fixed, rephrased to: "Two of the exposure periods are considered fixed and one not fixed".	Sentence adaptation	Minor
20	November 2022	9.3.1.1	Pregnancy for mother rephrased to "Pregnancy duration for mother".	Editorial change	Minor
21	November 2022	9.3.1.2	Pregnancy duration for mother was stated as a not fixed exposure period.	The sentence was adapted since pregnancy duration for mother in Sweden should be a not fixed exposure period	Minor
22	November 2022	9.3.1.3	Added: "• In this study, clusters of fathers with homogenous trajectories of drug intake during the assessment period will be identified, using the number of DDDs in every 14 days interval and grouping fathers with similar "trajectories" of this metric over time. Since it will be assumed that treated fathers will be exposed to 1 WHO DDD per day, the number of DDDs in each 14-days interval also coincides with the number of days covered in the same period (e.g. 10 DDDs = 10 days covered in a specific 14-days interval)." and "The K-means is a novel method	More detailed explanation of the K-means methods. The reference of Harault-Delarue supporting the explanation was already previously cited in the Protocol V5.0, and the reference ***Wood ME, Lupattelli A, Palmsten K, Bandoli G, Hurault-Delarue C, Damase-Michel C, et al. Longitudinal Methods for Modeling Exposures in Pharmacoepide***	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			applied in studies investigating medication safety during pregnancy as it can model complex real-world exposures. This method proposed by Hurault-Delarue et al. allows drug exposure during pregnancy to be modelled in a flexible way accounting for treatment intensity and evolution overtime. This methodology attempts to overcome some of the limitations associated with defining exposure using, for example binary classification (ever, never use) or the 'Intention To Treat' approach where dose is defined at one time point (e.g conception, or start of 3 months pre-conception period) since AED treatment may be modified if planning for,(or during) pregnancy. In particular, K-means has been used to identify trajectories of higher or lower medication exposure in studies investigating the effects of maternal exposure to medication during or after pregnancy on infant outcomes, with data from secondary databases (such as electronic health records, prescription orders or dispensation information). The application of this methodology for assessing paternal exposure in the population of this study is	***miologic Studies in Pregnancy. Epidemiol Rev. 2021 Jun 8***; was added	

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			novel, albeit follows the same principles."		
23	November 2022	9.3.2.3	**Case assessment** was redefined. Due to data access restrictions it was not possible to undertake manual assessment of computerized profiles of NDD cases identified through diagnostic codes. Therefore, the assessment will be undertaken on all NDD including ASD cases (not a sample as originally intended), based only on available coded data for the live birth offspring.	Adaptation. Please note the original plan was to conduct a manual assessment, so only 20% of cases was going to be included. Since the updated plan simply uses recorded data and the assessment will be done programmatically , all cases will be included	Minor
24	November 2022	9.7.1	Added the following text: The populations at study will include each individual offspring (or non-live birth) as the unit for analysis, therefore if the mother and father have more than one offspring they can be included more than once in the study; each offspring/non-live birth will coincide with the linked triple offspring/non-live birth, mother and father. Furthermore all variables collected for fathers and mothers will be re-calculated for each pregnancy.	Clarification on unit of analysis which is the offspring	Minor
25	November 2022	9.7.1	A legend was added in Table 7 "For CM only cumulative incidence proportion will be calculated".	Clarification of CM analysis	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
26	November 2022	9.7.2.2	In addition, cumulative incidence proportion for the entire period 0-12 years will also be presented; this will be calculated as the total number of offspring experiencing the outcome (NDD and CM, separately) during the entire follow-up (i.e. the sum of the number of events for the years 0 to 12) divided by the initial number of offspring included at the start of follow-up (i.e. population used in the analysis). Furthermore considering index date in the CM cohort will start before or on date of birth and that patients will be followed up until 12 years of age at maximum, there will be patients with a follow-up longer than 12 years, and therefore cumulative incidence proportion for the entire follow-up will include a longer period than 12 years (but shorter than 13 years)."	Clarification on cumulative incidence calculation	Minor
27	November 2022	9.7.3.2.1	Rephrased to "The PS score will be used in a weighted analysis instead of matched. The section was updated as follows (bold for additions and strikethrough for deletions): A crude and a propensity-score (PS) **weighted** (section 9.7.3.2.3) Cox Proportional Hazard (PH) regression model will be used to estimate the Hazard Ratios (HR) of NDD, including ASD, with 95% CI (using	During the development of the study analyses, PS models were estimated, and matching was conducted in one of the 3 countries. PS matching resulted in a reduction of the sample size between 40 and 50% (depending on which PS model was used);	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			offspring's calendar age in years as the underlying timescale) in offspring paternally exposed to valproate monotherapy within 3 months prior to LMP2 date compared to the reference group comprised of offspring paternally exposed to lamotrigine or levetiracetam (composite monotherapy) in the same time period. […] For purposes of the primary objective analysis for which the study is powered, a first Cox PH model will be estimated irrespective of clusters classification (section 9.3.1.3). This approach has the limitation to **ignore intensity of exposure in the two exposure groups**. To overcome this limitation, the first model will be repeated in**cluding the exposure intensity variable (estimated based** on clusters as by application of k-means methodology (section 9.3.1.3)) **as an effect modifier, i.e. the interaction exposure*k-means will be included in the model**. This second approach has the advantage of **providing an estimate of the effect of paternal exposure to valproate vs the comparator group stratified by exposure intensity as measured by the k-means clusters**."	considering the significant reduction due to the matching and the very low number of observed events in the primary and secondary outcome cohorts (these results have been provided in the interim report), it was decided that PS weighting should be used instead through the use of inverse probability of treatment weighting and that the effect estimation for both the primary and secondary outcome would be obtained in the weighted cohorts obtained using these PS weights	

Number	Date	Section	Description of change made	Justification	Minor or Major Change
28	November 2022	9.7.3.2.2	The PS score will be used in a weighted analysis instead of matched. The section was updated as follows (bold for additions and strikethrough for deletions): For purposes of the secondary objective analysis, a first logistic model will be performed ~~on all the PS matched units~~ irrespective of clusters classification (section 9.3.1.3). A second logistic model will be performed **including the exposure intensity variable (estimated based on** ~~using the PS matched units with a concordant classification in~~ clusters as by application of klmeans methodology (section 9.3.1.3)) **as an effect modifier, i.e. the interaction exposure*k-means will be included in the model** ~~stratified by cluster of homogeneous duration/intensity~~. Advantages and disadvantages of these approaches are reported in section 9.7.3.2.1.	Please see comment above	Minor
29	November 2022	9.7.4	For exploratory objective 5 there was rewording of this analysis. Where previous was "for offspring paternally exposed to AED polytherapy, summary cohort characteristics and univariate analysis will be performed to describe the subgroups and the risk factors for the primary	Clarification of the exposure groups in Exploratory analysis 5	

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			composite outcome (NDD, including ASD) and for the secondary composite outcome (CM) for offspring paternally exposed to valproate in combination with other AEDs excluding lamotrigine / levetiracetam (AED polytherapy) and offspring paternally unexposed to valproate but exposed to other AEDs (any combination) at the time of conception" it is now "for offspring paternally exposed to AED polytherapy, summary cohort characteristics and univariate analysis will be performed to describe the putative risk factors and frequency of the primary composite outcome (NDD, including ASD) and for the secondary composite outcome (CM) for offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine and levetiracetam) and offspring paternally exposed to levetiracetam/lamotrigine in polytherapy (i.e. polytherapy including at least one of them, and excluding valproate) at the time of conception.		
30	November 2022	9.7.6	• Sensitivity analysis 2 will be performed using the outcome of interest restricted to ASD specifically	Sensitivity analyses clarifications: • Sensitivity analysis 2 will it be	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			(ignoring all other NDD diagnoses). • Sensitivity analysis 6 will be performed comparing PS-weighted model, instead of PS matched model. • Sensitivity analysis 8 will be performed only in the Primary Outcome Cohort for Descriptive Analyses.	performed using the outcome of interest restricted to ASD. In this analysis, events for NDD other than ASD will be ignored; instead, only diagnoses for ASD will be considered as events (both in the descriptive analyses as well as in the comparative ones) • Sensitivity analysis 6 will compare the model of the main analysis with a covariate adjustment model, thus, the text was reworded to reflect the PS-weighted models that will be used in the main analysis • It was specified the cohort that will be used to assess the sensitivity analysis 8 will be conducted on primary outcome cohort only	

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			• Addition of a new sensitivity analyses (sensitivity analysis 11) that will use a narrow NDD composite case definition for primary outcome.	Addition of a new sensistivity analysis: • New sensitivity analysis (sensitivity analysis 11) Use of a narrow NDD composite case definition primary objective, exploratory objective 5 and 6	
31	November 2022	9.9.2	Clarification on additional conditions/events occurring during childhood that are associated with NDD/cognitive impairment such as Trisomy, some infectious diseases such as measles or meningitis, brain trauma, etc. These potential risk factors/confounders were not included in this study, but most probably would not lead to a differential bias across exposure groups.	Clarification on confounders/risk factors selection	Minor
32	November 2022	9.10.1	All post-approval changes are detailed in the present table.	Document consistency	Minor
33	November 2022	Annex 3	All codelists were updated to be consistent with codelists presented to PRAC in the Progress Report, dated 20 January 2021.	Document consistency. The updated codelist reflects the reality of databases and are the working codelists	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
34	July 2023	PASS information	PASS information was updated to remove PharmaSwiss, Biomo and Biogaran as they exited the Consortium.	Updated of MAH list	Minor
35	July 2023	PASS information	The Research Question and Objectives section was updated as follows (strikethrough for deletions): The aim of this retrospective cohort study is to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD, as well as CM in offspring. Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam ~~which are considered a safer treatment. In women these drugs are generally associated with lower risk of teratogenicity for the offspring but it is unknown whether there's a similar effect is the same in men~~.	Update as per PRAC request	Minor
36	July 2023	PASS information	Project team update.	Change of the IQVIA PI	Minor
37	July 2023	2	The list of abbreviations was updated to include all those reported in the document.	Editorial change	Minor
38	July 2023	3	The address of the contracting vendor and the PI were updated.	Change of the IQVIA address and PI	Minor
39	July 2023	4 (Rationale and background and	The date format was standardised to "DD Month YYYY"	Editorial change	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
		throughout the Document)	throughout the entire document.		
40	July 2023	4 (Overall aim)	The overall aim section was updated as follows (strikethrough for deletions): The aim of this retrospective cohort study is to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD, as well as CM in offspring. Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam ~~which are considered a safer treatment. In women these drugs are generally associated with lower risk of teratogenicity for their offspring but it is unknown whether there's a similar effect is the same in men~~.	Update as per PRAC request	Minor
41	July 2023	4 (Study design)	In Norway, the exposure information was updated to reflect the fact that it was derived from prescription data from 2008 and not from 2004.	Unavailability of Norwegian Patient Registry data before 2008. The updated exposure information reflects the reality of databases	Major
42	July 2023	4 (Variables: Secondary outcome)	CM will be evaluated within 12 years after birth for Denmark and within 10 years after birth for Norway. The Secondary outcome was updated as follows (bold for additions): CM will be evaluated as a composite endpoint among live	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month	Major

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			births within 12 years after birth **for Denmark and within 10 years after birth for Norway.**	lookback period for the study variables. The follow-up period for the offspring in Norway is up to maximum 10 years of age	
43	July 2023	4 (Milestones)	The study period for Norway was changed from 2006 to 2010. The text was updated as follows (bold for additions and strikethrough for deletions): Study period allowing 24 months prior to index date: from January 1997 (Denmark), January ~~2006~~**2010** (Norway) […].	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month lookback period for the study variables	Major
44	July 2023	8	The Research Question and Objectives section was updated as follows (strikethrough for deletions): The aim of this retrospective cohort study is to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD, as well as CM in offspring. Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam ~~which are considered a safer treatment. In women these drugs are generally associated with lower risk of teratogenicity for their offspring but it is unknown whether there's a similar effect is the same in men~~.	Update as per PRAC request	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
45	July 2023	9.1	In Norway, the exposure information was updated to reflect the fact that it was derived from prescription data from 2008 and not from 2004. The Study Design section was updated as follows (bold for additions and strikethrough for deletions): • Exposure information will be derived from prescription data, as recorded in the National Prescription Registries for each country (from 2005 in Sweden, ~~2004~~**2008** in Norway and 1995 in Denmark) to 31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway. • Figure 1 was modified. The text under "Follow-up and outcome ascertainment period" was modified as follows: From birth to the end of the study period or date of first diagnosis of neurodevelopmental disorders or death or emigration or age of 12 yo **for Denmark and Sweden or age of 10 yo for Norway.**	Unavailability of Norwegian Patient Registry data before 2008. The updated exposure information reflects the reality of databases	Major
46	July 2023	9.2.1	In Norway, the study time period was revised and initiated in 2010. The text was modified as follows (bold for additions and strikethrough for deletions): The study time period will be based on	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting	Major

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			availability of information from the National Registries; this will start from 01 January 2007 in Sweden, 01 January ~~2006~~**2010** in Norway, and 01 January 1997 (01April 2004 for secondary outcome) in Denmark in order to allow for 24 months average look back period for live births:...	in 2006 to ensure a 24-month lookback period for the study variables	
47	July 2023	9.2.3.1	In Norway, the follow-up period for the offspring was changed from birth to 12 years of age to birth to 10 years of age. The following text was modified as follows (bold for additions): • For the purpose of the evaluation of NDD, including ASD, Figure 3 illustrates the registry linkage of the study participants, the paternal exposure period (3-months prior to LMP2 date, for further details please see footnote 10), follow-up period for the offspring (from birth to maximum **12 years of age for Denmark and Sweden and 10 years of age for Norway**), and the look back periods for confounders for each linked family member (mother: 12 months prior to delivery, father: 12 months prior to LMP2 date).	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month lookback period for the study variables. The follow-up period for the offspring in Norway is up to maximum 10 years of age	Major

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			• Figure 3 was modified to specify a follow-up period **of ≤12 year for Denmark and Sweden and ≤10 year for Norway.**		
48	July 2023	9.2.3.1	The legend embedded within Figure 3 was updated: the abbreviation for AED was removed, as it was not utilized in the figure.	Editorial change	Minor
49	July 2023	9.2.3.2	In Norway, the follow-up period for the offspring was changed from 12 years of age to 10 years of age. The following text was modified as follows (bold for additions): • For the purpose of the evaluation of CM, Figure 4 and Figure 5 illustrate the registry linkage of the study participants, the paternal exposure period (3 months prior to LMP2 date), follow-up period for the offspring (from 12th or 22nd week of gestation, respectively, for Norway and Denmark and from birthdate of offspring for Sweden**,** to maximum 12 years of age for **Denmark and Sweden and 10 years of age for Norway**). • Figure 4 was modified to specify	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month lookback period for the study variables. The follow-up period for the offspring in Norway is up to maximum 10 years of age	Major

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			≤12 year follow-up time after birth **for Denmark and ≤10 year follow-up time after birth for Norway.**		
50	July 2023	9.2.3.2	The legends embedded within Figure 4 and Figure 5 were updated: the abbreviation for AED was removed as it was not utilized in the figures	Editorial change	Minor
51	July 2023	9.3.1	The Exposure and measures section was updated as follows (strikethrough for deletions): As reported in section 9.7.3.2, in the primary analysis, paternal exposure to valproate (monotherapy) will be compared to paternal exposure to lamotrigine or levetiracetam (composite monotherapy) ~~which are considered a safer treatment (10–13)~~.	Update according to the current evidence	Minor
52	July 2023	9.3.1.1	The legend embedded within Figure 6 was updated: the abbreviation for AED was added.	Editorial change	Minor
53	July 2023	9.3.1.2	The legend embedded within Figure 7 was updated: the abbreviation for AED was added.	Editorial change	Minor
54	July 2023	9.3.1.3	The legend embedded within Figure 8 was updated: the abbreviation for ATC and DDD were added.	Editorial change	Minor
55	July 2023	9.3.2.1	In Norway, the exit date/end of follow-up regarding reaching the age of 12 years was	Unavailability of Norwegian Patient Registry data before 2008.	Major

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			changed to reaching the age of 10 years. The following text was modified as follows (bold for additions): The exit date/end of follow-up will be defined as the end of the study period (31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway), death, emigration (where available), reaching the age of 12 years **for Denmark and Sweden and the age of 10 years for Norway** or date of first diagnosis of the outcome at study, which-ever is the soonest.	A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month lookback period for the study variables. The follow-up period for the offspring in Norway is up to maximum 10 years of age	
56	July 2023	9.3.2.2	In Norway, the exit date/end of follow-up regarding reaching the age of 12 years was changed to reaching the age of 10 years. The following text was modified as follows (bold for additions): The exit date/end of follow-up will be defined as the end of the study period (31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway), death, emigration (where available), reaching the age of 12 years **for Denmark and the age of 10 years for Norway**) or date of first diagnosis of the outcome at study, which-ever is the soonest.	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month lookback period for the study variables. The end of follow-up period for the offspring in Norway is, among the others listed that have not changed, reaching the age of 10 years	Major

Number	Date	Section	Description of change made	Justification	Minor or Major Change
57	July 2023	9.3.2.3	In Norway, the age of the offspring considered probable or possible case was changed to 10 years rather than of 12 years as in Denmark and Sweden. The following text was modified as follows (bold for additions): • ***Probable case:*** The offspring aged ≤12 years **for Denmark and Sweden and aged ≤10 years for Norway** will be considered a probable case if they satisfy the criteria that multiple diagnoses for NDD including ASD are recorded during follow-up, regardless of whether the same code is recorded multiple times or different codes are recorded. • ***Possible case:*** The offspring aged ≤12 years **for Denmark and Sweden and aged ≤10 years for Norway** will be considered a possible case if they satisfy the criteria that only one diagnosis record for NDD including ASD is recorded during follow-up.	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month lookback period for the study variables. The follow-up period for the offspring in Norway is ≤10 years	Major
58	July 2023	9.3.3	The abbreviations reported in the legends for Table 2, Table 3, and Table 4 were updated.	Editorial change	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
59	July 2023	9.4	Data from the Norwegian Patient Registry was available for record linkage since 2008. The following text was added to Table 5 (bold for additions): **Data available for record linkage since 2008.**	The updated text reflects the data availability for record linkage in Norway	Major
60	July 2023	9.4 – 9.5 – 9.7.1	• The position of the titles for Table 5, Table 6, and Table 7 was moved from below the bodies of the tables to above them. • The abbreviations reported in the legends for Table 5 and Table 7 were updated.	Editorial change	Minor
61	July 2023	9.7.2.2	The entire period for the cumulative incidence proportions in Norway was changed from 0-12 years to 0-10 years. The following text was modified as follows (bold for additions): • In addition, cumulative incidence proportions for the entire period, 0-12 years **for Denmark and Sweden and 0-10 years for Norway**, will also be presented; this will be calculated as the total number of offspring experiencing the outcome (NDD and CM, separately) during the entire follow-up (i.e., the sum of the number of events for the years 0	Unavailability of Norwegian Patient Registry data before 2008. A revised study period starting in 2010 was used instead of starting in 2006 to ensure a 24-month lookback period for the study variables. The entire follow-up period for the offspring in Norway is 0-10 years	Major

Number	Date	Section	Description of change made	Justification	Minor or Major Change
			to 12 **for Denmark and Sweden, and 0 to 10 for Norway**) divided by the initial number of offspring included at the start of follow-up (i.e., population used in the analysis). • Furthermore considering index date in the CM cohort will start before or on date of birth and that patients will be followed up until 12 years of age at maximum (**10 years of age for Norway**), there will be patients with a follow-up longer than 12 years (**10 years for Norway**), and therefore cumulative incidence proportion for the entire follow-up will include a longer period than 12 years for Denmark and Sweden (but shorter than 13 years). • **For Norway, the cumulative incidence proportion for the entire follow-up will include a longer period than 10 years, but shorter than 11 years.**		
62	July 2023	Annex 3	All tables were formatted, and the legends were included, which report the abbreviations used within the tables.	Editorial change	Minor

Number	Date	Section	Description of change made	Justification	Minor or Major Change
63	July 2023	Annex 4	Table 62 was updated to remove PharmaSwiss, Biomo and Biogaran as they exited the Consortium.	Update of MAH list	Minor
64	August 2023	Abstract: Milestones	Milestones were updated to include additional deliverables, in addition to the original final report of study results, for version 1.1. This version represents the second submission.	Update of deliverables and submission date	Minor
65	August 2023	Milestones	Table 1 was updated to include additional deliverables, in addition to the original final report of study results, for version 1.1. This version represents the second submission.	Update of deliverables and submission date	Minor
66	August 2023	Rationale, Research question and objectives	The following text was modified as follows (strikethrough for deletions): Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam. ~~which are considered a safer treatment (10-13). In women these drugs are generally associated with lower risk of teratogenicity for their offspring but it is unknown whether there effect is the same in men.~~	Update as per PRAC request	Minor
67	September 2023	PASS Information	MAH participating in Consortium.	Update of MAH list	Minor

6. MILESTONES

A progress report is planned 12 months after PRAC endorsement of protocol (Q1 2021) with an interim 6 months after (predicted to be for Sweden and Norway). Due to the long and unknown timeline for data approval, especially in Denmark, the final study report is planned for 23 January 2023. This is because the ethics and data request process in the countries of interest has been known to take anywhere from 6 to 20 months in some cases. Obtaining the data is a pivotal part of producing the interim and final reports. For this reason we propose a progress report, one interim report and one final report (Table 1).

Table 1: Key milestones

Milestone	Planned date
Registration in the EU PAS register	Q1 2020 (after endorsement of protocol and before data extraction)
Start of data extraction	Q4 2020
End of data extraction	Q1 2021
Progress report	Q1 2021 (12 months after PRAC endorsement)
Interim report	Q3 2021 (Country-specific)
Final report of study results	23 January 2023, in accordance with PRAC
Final report of study results v1.1, second submission	27 March 2023
Addendum to the final report of study results v1.1 (report on sensitivity analysis 2 and exploratory analysis 8)	27 March 2023
Annex to the final report of study results v1.1 (compilation of sensitivity analysis tables)	27 March 2023
Request for Amendment received from PRAC	05 May-13 June 2023
Partial Responses to List of PRAC Questions	10 July 2023
Submission of the deliverables related to results of the Norwegian re-run analyses	Due 23 October 2023
Submission of updated protocol v7	Due 23 October 2023

EU: European Union; PAS: Post-Authorisation Study; PRAC: Pharmacovigilance Risk Assessment Committee

The conditions to market authorisation require that the study protocol is submitted in accordance with article 107n (1) of directive 2001/83/ec within 6 months after commission decision (received on 31 May). A progress report shall be submitted to the PRAC within 12 months after PRAC endorsement. An interim report will be submitted to the PRAC 6-months after, and the final report in the 23 January 2023, as in accordance with PRAC.

7. RATIONALE AND BACKGROUND

7.1 Background

Valproate-containing medicines are approved nationally in the EU to treat epilepsy and bipolar disorder. It is also approved in some countries for prevention of migraine, but not supported by all MAHs. In recent years, due to an increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD), and congenital malformations (CM) in offspring after valproate exposure in utero, the use of valproate has been restricted to cases in which no other effective or tolerated treatment is available in women of childbearing potential or in pregnant women suffering from epilepsy; it has been contraindicated in pregnant women suffering from bipolar disorder (2).

While the effects of maternal exposure of drugs during pregnancy on offspring outcomes are widely studied, the role of paternal exposure to drugs prior to conception on offspring's health has not yet been clearly demonstrated. Evidence from paternal exposure to radiation, antimitotic drugs or environmental toxins suggest that (epi-)genetic modifications may be transmitted through the father to the next generation. Engeland et al. studied the possible association between drugs dispensed to the father in the 3 months prior to conception and adverse pregnancy outcomes (3), with no strong conclusion.

Previous literature found that paternal exposure to valproate in mice might lead to behavioral alterations in offspring (4). It is still unclear if these results may be translated to the human population.

The spermatogenic cycle in humans lasts about 74 days (2.5 months) (5), which may be a vulnerable time for acute exposures such as drug intake. Large population-based studies addressing the associations between increased risk of adverse outcomes in the offspring following paternal exposure to drugs prior to conception are rare, as few databases offer the possibility of paternal-offspring linkage, and the effect of the paternal exposure may be very small. Thus far, only one study based on Danish national registers has reported an increased risk of ASD following paternal use of selective serotonin reuptake inhibitors (SSRIs) before conception (6), and concluded that the increased risk of ASD in the offspring associated with paternal SSRI use before conception may be attributable to paternal underlying psychiatric indications related to SSRI use or other unmeasured confounding factors. Other studies which evaluated the paternal exposure to Disease-Modifying Antirheumatic Drugs in Norwegian registries (7), or a large number of different prescription drugs in Norwegian registries including antiepileptic drugs (AEDs) (3,8), did not find an increased risk for adverse outcomes in offspring. Specifically, the risk of paternal exposure to valproate has thus far not been found to significantly affect offspring's outcomes (3,9).

7.2 Rationale

There is currently scarce real-world evidence of an increased risk of NDD including ASD, or CM in offspring following paternal exposure to AEDs. Therefore, following the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation dated 08 February 2018, this post-authorisation safety study (PASS) is being conducted to evaluate the association between paternal exposure to valproate and risk of NDD, including ASD, as well as CM in offspring.

8. RESEARCH QUESTION AND OBJECTIVES

The aim of this retrospective cohort study is to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD, as well as CM in offspring. Paternal exposure to valproate will be compared to paternal exposure to lamotrigine or levetiracetam.

Primary objective

1. Investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.

Secondary objectives

2. Investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception, in Norway and Denmark.
3. Describe AED exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort.
4. Identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine or levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers.

Exploratory objectives

5. To describe the putative risk factors and frequency of NDD, including ASD, as well as CM in offspring paternally exposed to valproate (in combination with other AEDs) and to other AEDs (in combination with other AEDs, excluding valproate) at the time of conception.
6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception.
7. Investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception in Sweden.
8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.

9. RESEARCH METHODS

9.1 Study Design

The study will be carried out using a retrospective non-interventional longitudinal population-based cohort design conducted using secondary data derived from multiple registry databases recording longitudinal medical data in Sweden, Norway, and Denmark. The aim is to study the risk of NDD including ASD, as well as CM in offspring following paternal exposure to valproate.

For the evaluation of NDD, including ASD, the population for analysis will be comprised of live births for whom medical record linkage to mother and father is available within such registries. For the evaluation of CM, the population for analysis will be comprised of live births, stillbirths and spontaneous abortions[2] during gestation (2nd and 3rd trimester) for whom medical record linkage to mother and father is available within such registries, for Norway and Denmark. For Sweden the corresponding population for analysis will be comprised of live births only. The primary outcome of interest is NDD, including ASD in offspring up to 12 years of age based on ICD-10 diagnostic codes, as recorded in the National Patient Registries. The secondary outcome of interest is a composite of CM diagnosed in offspring up to 12 years of age, stillbirths and spontaneous abortions-based on ICD-10 diagnostic codes, as recorded in the National Patient Registries and Medical Birth Registries. The primary exposure of interest is paternal use of valproate during the spermatogenic risk window prior to conception of the offspring (defined by the first day of the last menstrual period date plus two weeks [LMP2] of the mother within the linked family unit). Exposure information will be derived from prescription data, as recorded in the National Prescription Registries for each country (from 2005 in Sweden, 2008 in Norway and 1995 in Denmark) to 31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway. Country-specific cohorts of eligible linked family units will be identified. These cohorts (in terms of aggregated results) will be combined into an all-Nordic cohort (Sweden, Norway, Denmark for the primary outcome and Norway, Denmark for the secondary outcome) where feasible to further increase validity and statistical power. An overview of the study design for the primary and secondary outcomes are provided in Figure 1 and Figure 2.

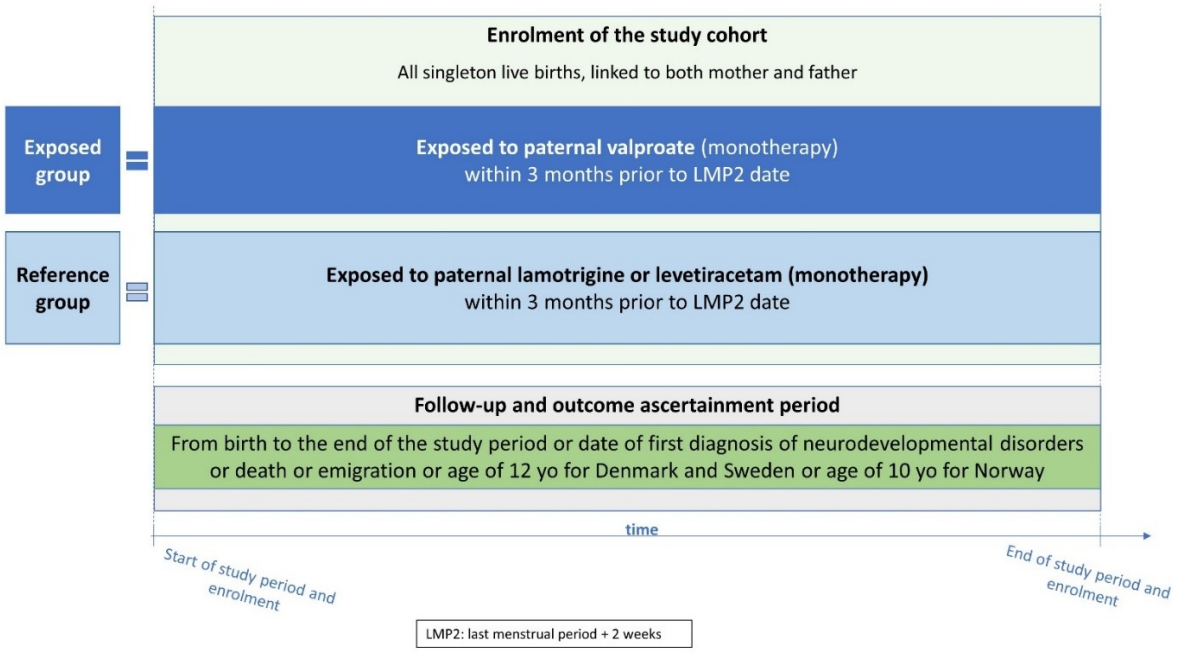

Figure 1: Overview of the study design for evaluating the primary outcome

[2] Data about voluntary or medically required abortions, that can have a diagnosis of CM, are not linked to fathers in none of the countries at study.

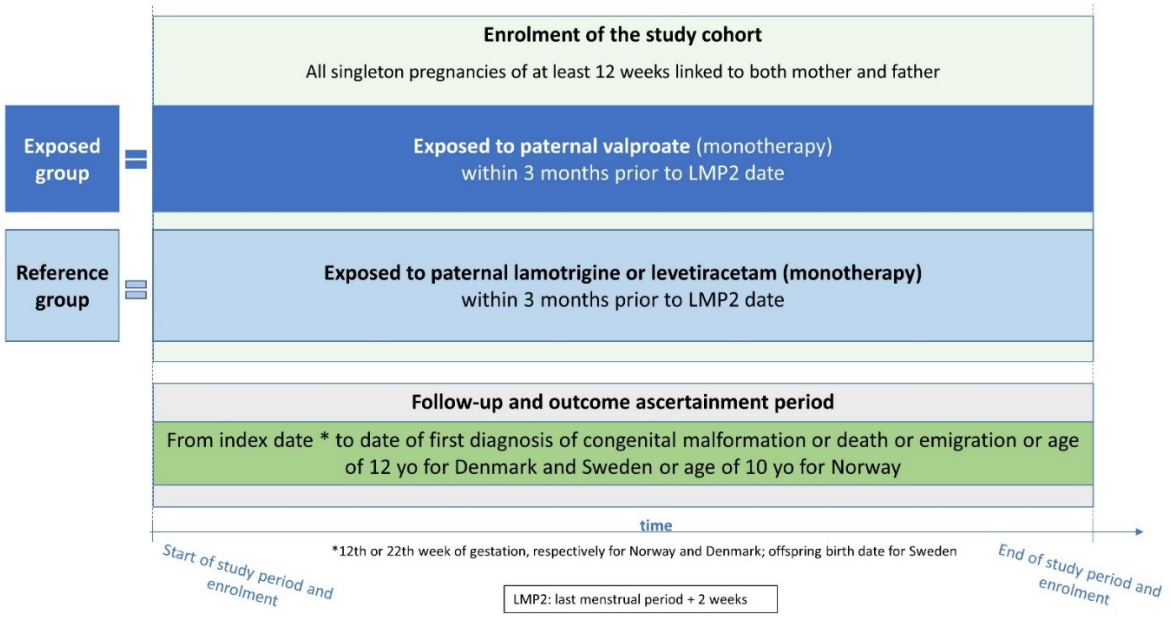

Figure 2: Overview of the study design for evaluating the secondary outcome

9.2 Setting

For real-world evidence generation, secondary longitudinal data sources can offer insights into clinical characteristics and outcomes. However, linkage of fathers to offspring is rare in most European countries, as typically only the mother is linked to the offspring within the data. It is also rarely noted in the record of a man, that they became a father. The exception of this are Scandinavian countries, which offer the possibility to link paternal data to offspring using national identification numbers and registers. This study widens the population size and broadens the geographic scope compared to the previous studies on valproate and offspring outcomes (10–13). This study will therefore focus on the three Scandinavian countries: Sweden, Denmark, and Norway.

9.2.1 Study time period

The study time period will be based on availability of information from the National Registries; this will start from 01 January 2007 in Sweden, 01 January 2010 in Norway, and 01 January 1997 (01 April 2004[3] for secondary outcome) in Denmark in order to allow for 24 months average look back period for live births:

- pregnancy duration (9-months on average for live births),
- maternal and paternal preconceptional exposure (3-months),
- minimum look back period for confounders (12-months).

The study time period ends on 31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway. The rationale for this choice is to include all data available from relevant

[3] In Denmark, for the period 1997-1 April 2004, stillborns born between 22nd and 28th weeks of gestation are not included in the Medical Birth Register but in the National Patient Register. However, since in the National Patient Register the linkage with the father is not available, the study period for the secondary outcome in Denmark is limited to 2004-2017 (or last available date).

linked registers, to capture a sufficient number of outcomes and exposures and linked family units, and to include the most up-to-date data available.

9.2.2 Participants

Since this is a non-interventional observational study, minimal inclusion and exclusion criteria are desirable to minimise potential selection bias and represent real clinical practice. The following selection criteria will be applied for the data extraction:

Inclusion criteria for data extraction

- Singleton[4] pregnancies, with known pregnancy-length of at least 12 weeks[5] within the study time period;
- Pregnancies linked to both mother and father within the study time period;
- Father with a continuous enrolment[6] in the database for ≥12 months prior to linked mother LMP2 date;
- Father with at least one AED in the data available.

For Sweden the inclusion criteria are slightly different, as only live births can be included:

- Singleton[4] pregnancies resulting in live births
- Pregnancies linked to both mother and father within the study time period;
- Father with a continuous enrolment in the database for ≥12-months prior to linked mother LMP2 date;
- Father with at least one exposure to AED during 192 days prior to 28 days after LMP2 date

Exclusion criterion for data extraction

- Adopted children
- Pregnancy associated with in vitro fertilisation (IVF)
- Pregnancies with missing gestational age and/or missing maternal LMP2 (for these pregnancies it will not be possible to identify the exposure window for the study)

To address the research questions related to the primary outcome (NDD including ASD) and secondary outcome (CM) two separate cohorts will be created, and additional selection criteria, nested within the criteria for data extraction, will be applied (see Section 9.2.2.1). These cohorts will from now on be referred as the primary and secondary outcome cohort.

[4] Twins were excluded because they share the same paternal exposure and it is not known how medication can be absorbed, distributed and metabolised by each of them. Moreover preterm birth and low birth weight (associated with NDD and CM) occur more frequently in twin and triplet pregnancies than in singleton pregnancies.

[5] Pregnancy terminations (e.g. spontaneous abortions) before 12 weeks gestation are not recorded in the data sources.

[6] A patient is considered continuously enrolled in a specific time period if that patient had a contact with healthcare services (such as drug prescription or hospitalisation) prior to that period and if emigration or death were not notified after this contact.

9.2.2.1 Neurodevelopmental disorders, including ASD

The following inclusion and exclusion criteria will be applied, after data extraction, to create a family linked cohort with the objective of investigating the risk of NDD, including ASD, in offspring paternally exposed to valproate.

Inclusion criteria for the primary outcome cohort

- Singleton born alive[7] within the study time period (i.e. the birth of only one child during a single delivery)
- Mother with a continuous enrolment[8] for ≥12-months prior to child birthdate

Exclusion criteria for the primary outcome cohort

- Offspring whose parent(s) have a history of CM or NDD (according to available records)

9.2.2.2 Congenital malformations

The following inclusion and exclusion criteria will be applied, after data extraction, to create a family linked cohort with the objective of investigating the risk of CM in offspring paternally exposed to valproate.

Inclusion criterion for secondary outcome cohort

- Mother with a continuous enrolment[9] of 12-months prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark, and birthdate of live offspring in Sweden)

Exclusion criterion for secondary outcome cohort

- Offspring whose parent(s) have a history of CM or NDD (according to available records)

9.2.3 Overview of the family linkage

9.2.3.1 Neurodevelopmental disorders, including autism

For the purpose of the evaluation of NDD, including ASD, Figure 3 illustrates the registry linkage of the study participants, the paternal exposure period (3-months prior to LMP2 date, for further details please see footnote 10), follow-up period for the offspring (from birth to maximum 12 years of age for Denmark and Sweden and 10 years of age for Norway), and the look back periods for confounders for each linked family member (mother: 12 months prior to delivery, father: 12 months prior to LMP2 date).

[7] Non-live births are not included because a diagnosis of NDD cannot be made

[8] A patient is considered continuously enrolled in a specific time period if that patient had a contact with healthcare services (such as drug prescription or hospitalisation) prior to that period and if emigration or death were not notified after this contact.

[9] A patient is considered continuously enrolled in a specific time period if that patient had a contact with healthcare services (such as drug prescription or hospitalisation) prior to that period and if emigration or death were not notified after this contact.

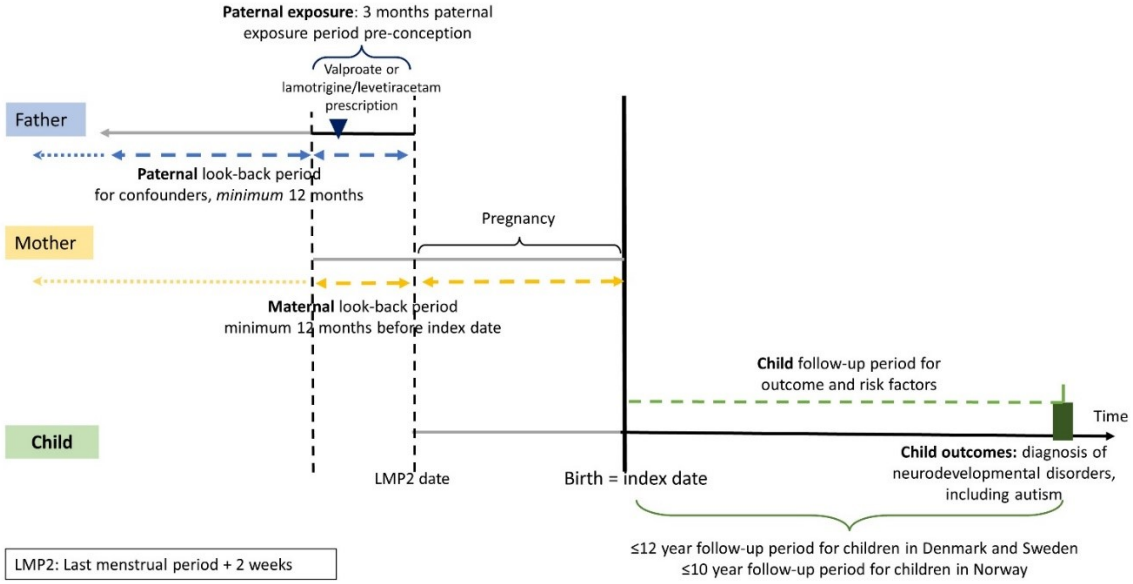

Figure 3: Overview of the family linkage, NDD including ASD

9.2.3.2 Congenital malformations

For the purpose of the evaluation of CM, Figure 4 and Figure 5 illustrate the registry linkage of the study participants, the paternal exposure period (3 months prior to LMP2 date), follow-up period for the offspring (from 12th or 22nd week of gestation, respectively, for Norway and Denmark and from birthdate of offspring for Sweden, to maximum 12 years of age for Denmark and Sweden and 10 years of age for Norway), and the look back periods for confounders for each linked family member (mother: minimum of 12 months prior to index date, father: minimum of 12 months prior to LMP2 date).

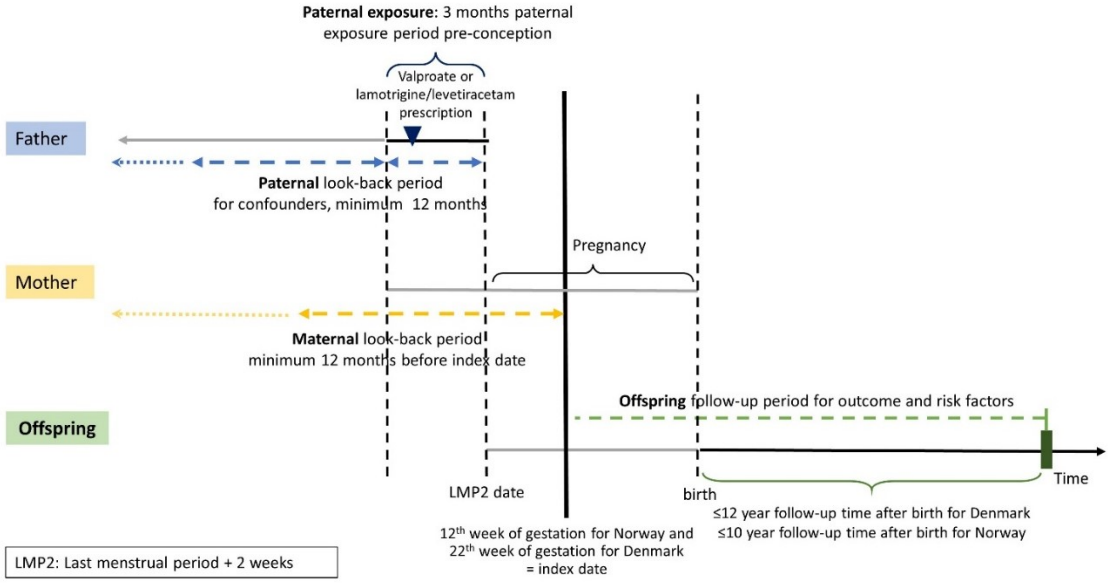

Figure 4: Overview of the family linkage, CM for Norway and Denmark

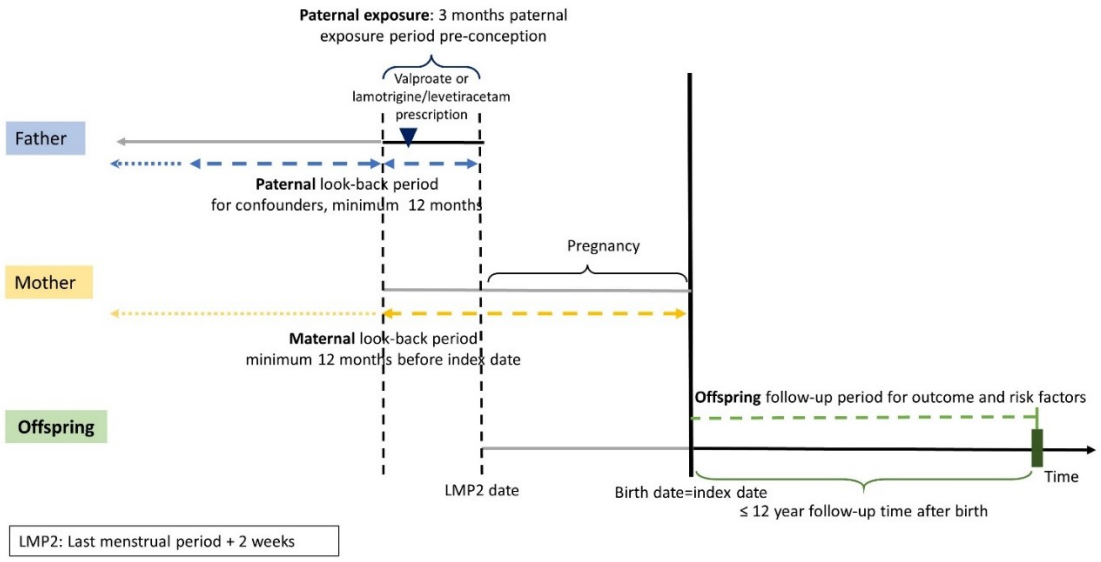

Figure 5: Overview of the family linkage, CM for Sweden

9.3 Variables

In order to meet the study objectives, the following parameters will be obtained from the selected data sources and analysed:

- Demographic characteristics for descriptive cohort
- Exposure of interest (section 9.3.1)

- Outcome parameters of interest (section 9.3.2)
- Potential confounding variables (section 9.3.3)

9.3.1 Exposure definition and measures

Within the AEDs, the primary exposure of interest is the dispensation of valproate. Brand names and generics of all forms of valproate salts will be considered (sodium valproate, valproic acid, valproate semisodium and valpromide) and summarized under the term "valproate". Valproate will be identified using Anatomical Therapeutic Chemical (ATC) code N03AG01.

Drug exposure of the offspring is based on the use of AEDs by the father during a risk window prior to conception. Since the spermatogenic cycle is approximately 2.5 months, *the risk window considered here is three months prior to conception*. Further details are presented in section 9.3.1.3

As reported in section 9.7.3.2, in the primary analysis, paternal exposure to valproate (monotherapy) will be compared to paternal exposure to lamotrigine or levetiracetam (composite monotherapy). These drugs are generally associated with lower risk of teratogenicity for the offspring of women, however it is unknown whether the effect is the same in men. Lamotrigine and levetiracetam will be identified using ATC codes N03AX09 and N03AX14, respectively. Since polytherapy is indicated for medically refractory epilepsy (14), in order to avoid the risk of disease severity bias associated to polytherapy, evaluation of AED exposure according to monotherapy is preferred for comparative analyses. In this section, definitions of monotherapy and polytherapy are only discussed for AEDs. Co-medications (other than AEDs) are defined in section 9.3.3 (Potential confounding variables). Monotherapy is defined as the exposure to a single AED, whilst polytherapy is defined as any combination of AEDs (including valproate among the exposed and excluding valproate among the unexposed), simultaneously or in sequence, within the 3-months risk window. For example, switching to or switching from an AED other than valproate, lamotrigine or levetiracetam, will be considered as polytherapy, and the offspring of these fathers will be excluded from the comparative analyses. This is because a washout period is not possible in clinical practice since subjects may not be unexposed for seizure control. Including people who were exposed to more drugs of the same class, in the period of interest, could lead to uncertainty in defining which drug is associated with the outcome.

Paternal exposure to other AEDs except valproate during the 3-months risk window and also maternal and offspring exposure (section 9.3.3) to AEDs will be elucidated.

Other AEDs will be identified using ATC codes (full list defined in Annex 3. Additional Information) and include:

- N03AA - Barbiturates and derivatives
- N03AB - Hydantoin derivatives
- N03AC - Oxazolidine derivatives
- N03AD - Succinimide derivatives
- N03AE - Benzodiazepine derivatives
- N03AF - Carboxamide derivatives
- N03AG (excluding N03AG01) - Fatty acid derivatives

- N03AX (excluding N03AX09 and N03AX14) - Other antiepileptics

Different AED exposure periods are applied for the father, mother and offspring, and also for NDD (including ASD) and CM for Norway and Denmark, as shown in Figure 6 and Figure 7, respectively. For the CM analysis for Sweden, the exposure periods correspond to those specified for NDD (Figure 6). *The paternal exposure to AEDs is the exposure of interest in this study, whereas maternal and offspring exposure to AEDs are potential risk factors.* Methodologies related to the maternal and offspring exposure will be further discussed in Section 9.3.3.

9.3.1.1 Neurodevelopmental disorders, including autism

Two of the exposure periods are considered fixed and one not fixed.
Fixed exposure periods:

- 3-months[10] pre-conception for father (due to spermatogenic cycle)
- 3-months pre-conception for mother (section 9.3.3)

Not fixed exposure periods:

- pregnancy duration for mother (section 9.3.3)

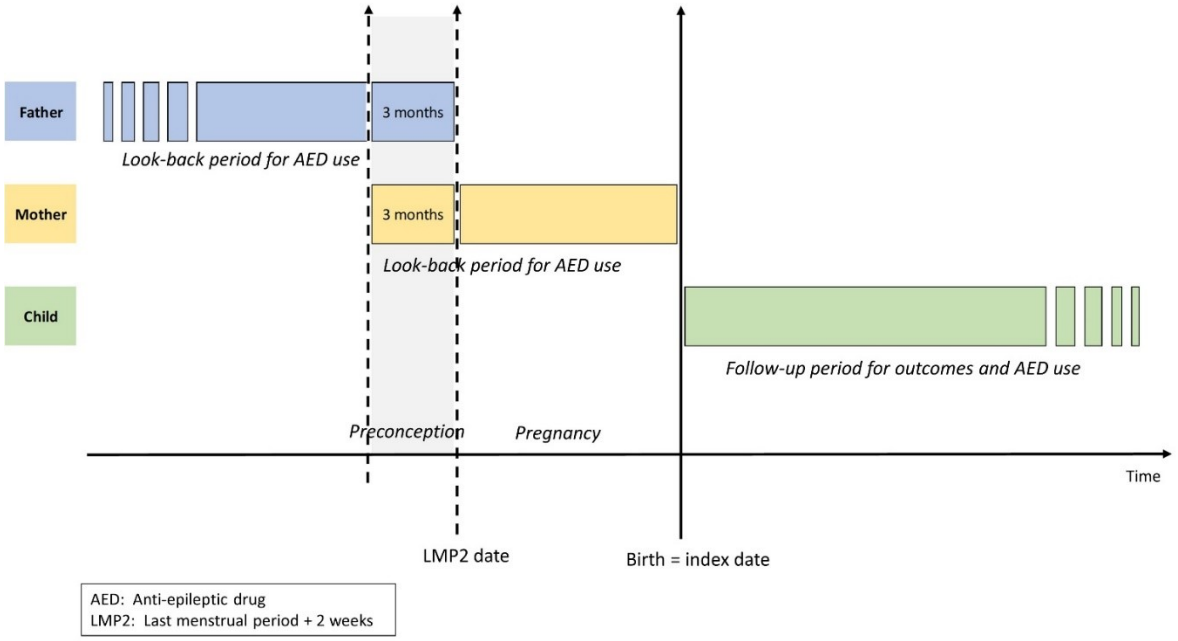

Figure 6: Treatment exposure windows, NDD including ASD; CM for Sweden only

[10] In order to account for potential dispensations that can have led to an intake during the 3 months look-back period under investigation, all dispensations that are recorded in the 6 months before conception that gave rise to an AED intake during the 3 months prior to conception will be considered. Because information on the exact number of days supplied is not available, patients' drug use periods will be calculated using the defined daily doses (DDD) metric as defined by the World Health Organization. For each prescription the total number of DDDs will be translated into the number of days in which the patient was treated, counting 1 DDD per day and distributing all available DDDs to the days of follow-up and allowing for the use of accumulated DDDs over time.

9.3.1.2 Congenital malformations

All the exposure periods are considered fixed, except one :

- 3-months[11] pre-conception for father (due to spermatogenic cycle)
- 3-months pre-conception for mother (section 9.3.3)
- 12 or 22 weeks prior to index date for mother, respectively in Norway and Denmark (section 9.3.3)

Not fixed

- pregnancy duration for mother, in Sweden (section 9.3.3)

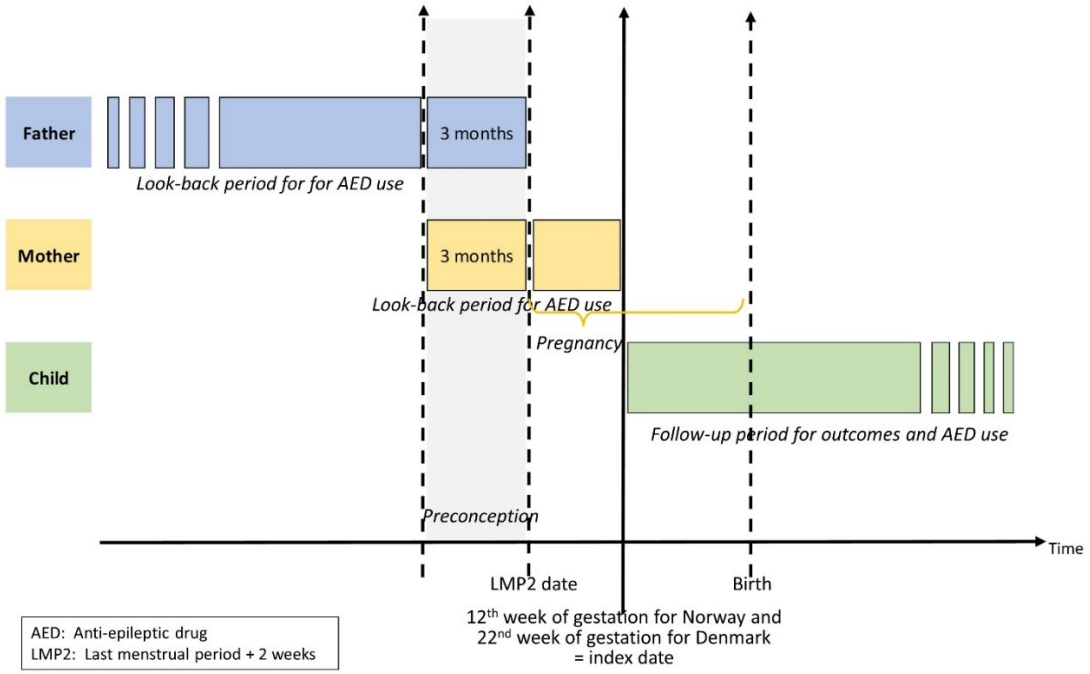

Figure 7: Treatment exposure windows, CM for Norway and Denmark

9.3.1.3 Classification of exposure

Particular care will be taken in the definition and classification of paternal exposure. Person-time exposed will be classified to take into account intensity of drug exposure during the 3-months pre-conception risk window using the longitudinal K-means clustering (R package kml) algorithm (15). This method allows for a more precise description of exposure of fathers to drugs and allows profiles to be distinguished improving evaluation of effects of drugs on outcomes. In summary the following steps apply:

- To quantify drug exposure, for each individual, prescription data will be transformed into the standard units of measurement of the World Health Organization (WHO): the Defined Daily Dose (DDD) (Figure 8). The duration of treatment and dates of exposure

[11] See footnote 10

will be estimated assuming individuals are exposed to one DDD per day and using information on number of units and dates of prescriptions, where available. For the father, drug prescribed and dispensed three months before the LMP2 date (including the LMP2 date) will be taken into account. A validation of the assumption that individuals are exposed to one DDD per day will be provided as a sensitivity analysis (section 9.7.5).

- After super imposing length of exposure onto the spermatogenic risk window, exposure data will be individually transformed into number of DDDs (Figure 8) dispensed during every 14 day interval within the 3-months exposure period. This way, the cumulative drug exposure of each father will be evaluated at several time points, and the exposure data will become longitudinal which will allow drawing individual trajectories of exposure through the pre-conception period. Data will be censored at the LMP2 date.
- In this study, clusters of fathers with homogenous trajectories of drug intake during the assessment period will be identified, using the number of DDDs in every 14 days interval and grouping fathers with similar "trajectories" of this metric over time. Since it will be assumed that treated fathers will be exposed to 1 WHO DDD per day, the number of DDDs in each 14-days interval also coincides with the number of days covered in the same period (e.g. 10 DDDs = 10 days covered in a specific 14-days interval). The longitudinal K-means clustering algorithm will be applied to create K clusters with homogenous trajectories, as empirically driven by the data. No assumption about the number of clusters is made prior to running the algorithm. Mean DDD trajectories will be plotted for each cluster and shape described. It is anticipated that several clusters of exposed fathers will be identified with homogenous trajectories of exposure during the 3-months risk window. For example, Cluster A = low constant exposure, Cluster B = decreasing exposure, Cluster C = moderate constant exposure, Cluster D = increasing exposure and Cluster E = high constant exposure.

  The K-means is a novel method applied in studies investigating medication safety during pregnancy as it can model complex real-world exposures. This method proposed by Hurault-Delarue et al.(15) allows drug exposure during pregnancy to be modelled in a flexible way accounting for treatment intensity and evolution overtime. This methodology attempts to overcome some of the limitations associated with defining exposure using, for example binary classification (ever, never use) or the 'Intention To Treat' approach where dose is defined at one time point (e.g conception, or start of 3 months pre-conception period) since AED treatment may be modified if planning for,(or during) pregnancy.

  In particular, K-means has been used to identify trajectories of higher or lower medication exposure in studies investigating the effects of maternal exposure to medication during or after pregnancy on infant outcomes, with data from secondary databases (such as electronic health records, prescription orders or dispensation information) (16). The application of this methodology for assessing paternal exposure in the population of this study is novel, albeit follows the same principles.
- Descriptive statistics will summarise distribution of exposure to each AED within each cluster.
- The empirically defined clusters will be used in the analyses of the study objectives. In the comparative analyses the exposure will be expressed as a dichotomous variable: exposure to valproate in monotherapy vs exposure to lamotrigine/levetiracetam in

monotherapy. The classification in cluster identified with the longitudinal K-means algorithm will be used to stratify the comparative analysis in cluster homogeneous for duration and intensity of exposure.

The K-means algorithm will be applied to maternal exposure within the 3-months period prior to LMP2 and during the reported period of gestation. However, since mothers exposed to AEDs will be excluded from the comparative analyses, these data will only be provided for descriptive purposes.

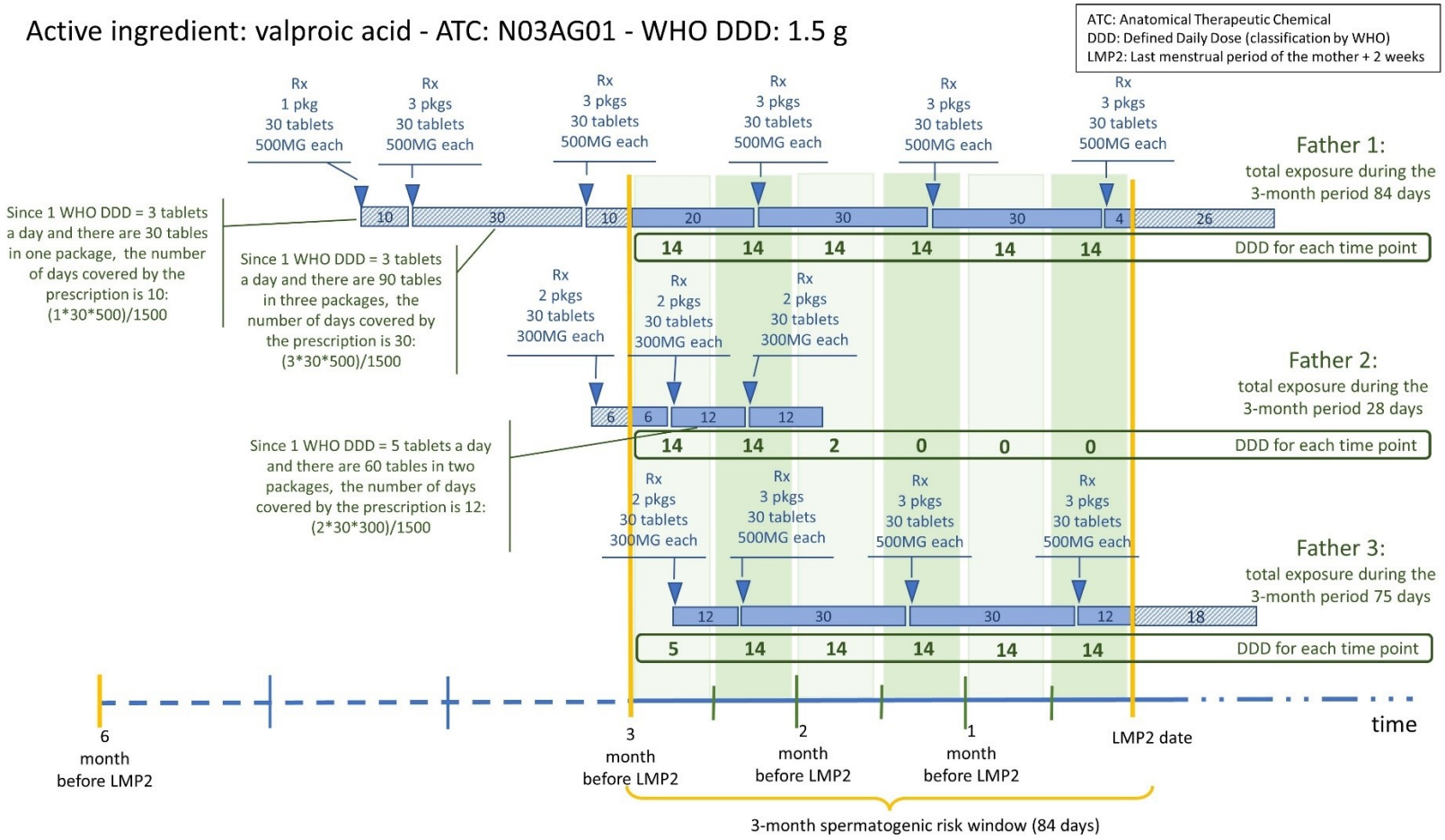

Figure 8: Calculation of paternal exposure in each 14-day interval during the 3-months risk window prior to conception

9.3.2 Outcome definition and measures

During the observation period, which will span from the index date to the exit date for each offspring, outcome events will be identified based on ICD-10 codes recorded inpatient registries.

9.3.2.1 Neurodevelopmental disorders, including ASD

The **index date** will be defined as the birth date of the offspring from which offspring will be observed for occurrence of the outcome of interest[12].

The **exit date/end of follow-up** will be defined as the end of the study period (31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway), death, emigration (where available), reaching the age of 12 years for Denmark and Sweden and the age of 10 years for Norway or date of first diagnosis of the outcome at study, which-ever is the soonest.

The primary outcome is NDD including ASD, will be defined as a diagnosis of at least one the ICD-10 codes presented in codelist Table 10. Please note that ASD codelist is presented separately in the codelist Table 8, and NDD without ASD in the codelist Table 9.

9.3.2.2 Congenital malformations

With the objective of investigating the risk of CM in offspring paternally exposed to valproate, all CM will be included in the comparative analysis, with the caveat that minor CM are usually under reported, therefore estimates could be under-estimated (17). However, a sensitivity analysis will be performed to address this concern (see section 9.7.5, *Broader definition of CM for secondary outcome*), for Norway and Denmark only.

The **index date (start of follow-up)** will be defined as the start of the 2nd trimester or 3rd trimester (12th or 22nd week of gestation), respectively for Norway and Denmark, and from offspring birth date for Sweden from which pregnancies will be followed up for the outcome of interest.

The **exit date/end of follow-up** will be defined as the end of the study period (31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway), death, emigration (where available), reaching the age of 12 years for Denmark and the age of 10 years for Norway) or date of first diagnosis of the outcome at study, which-ever is the soonest.

The analysis of the secondary outcome of CM will be defined according to the presence of at least one of the following criteria:

- an ICD-10 code of CM among live births
- an ICD-10 code of CM in diagnosis/reason for spontaneous abortion/stillbirth (Norway and Denmark only)

The analysis will focus on all CMs, with further substratification by body system organ class[13]. The ICD-10 codes for all CMs are are presented in codelist Table 11.

---

[12] Period between LMP2 (date of conception) and date of birth is immortal - child must survive to be eligible and diagnosis of ASD cannot occur *in utero*

[13] CM will be classified according to the EUROCAT categories Guide 14 (section 3.3 in EUROCAT Subgroups of congenital anomalies (18)).

9.3.2.3 Case assessment

This will be undertaken to further assess offspring that will be identified as cases with the primary outcome of interest (NDD including ASD).

Due to data access restrictions it is not possible to undertake **manual** assessment of computerized profiles of NDD cases identified through diagnostic codes. Therefore, the assessment will be undertaken on all NDD including ASD cases (not a sample as originally intended), based only on available coded data for the live birth offspring.

The clinical code list for NDD including ASD refers to the following categories (please see Table 10):

- Intellectual disabilities
- Communication disorders
- Disorders of psychological development
- Hyperkinetic disorders
- Tic disorders
- Movement disorders

Population

All offspring from the Primary Outcome Cohort for Descriptive Analyses who will be identified as having the outcome of interest (NDD including ASD).

Please note the original plan was to conduct a manual assessment, so only 20% of cases was going to be included. Since the updated plan simply uses recorded data and the assessment will be done programmatically, all cases will be included.

Methods

Each offspring that will be identified as a case of NDD including ASD will be assessed, and categorized into one of the following categories:

Probable case: The offspring aged ≤12 years for Denmark and Sweden and aged ≤10 years for Norway will be considered a probable case if they satisfy the criteria that multiple diagnoses for NDD including ASD are recorded during follow-up, regardless of whether the same code is recorded multiple times or different codes are recorded

Possible case: The offspring aged ≤12 years for Denmark and Sweden and aged ≤10 years for Norway will be considered a possible case if they satisfy the criteria that only one diagnosis record for NDD including ASD is recorded during follow-up

Percentage of probably and possible cases across all exposure categories will be reported. The percentages of number of offspring identified as cases of NDD including ASD will be calculated over the total pregnancies in each group. The percentages of probable and possible cases will be calculated over the total number of offspring identified as cases of NDD including ASD in each group.

“Non-cases” will not be captured since the analysis focuses on offspring with at least one record indicating NDD including ASD.

9.3.3 Potential confounders/risk factors

A broad range of risk factors and potential confounders, related to the offspring, father and mother, will be considered in the multivariable analysis. These include, but are not limited to, demographic and clinical characteristics and concomitant medications. The final choice of confounders will depend on the availability of data, clinical relevance and model fit.

The list of potential risk factors and potential confounders for NDD and CM are summarised below in Table 2, Table 3, Table 4 with further detail found in Annex 3. Additional Information. Factors listed as exclusion criteria for the comparative, sensitivity and exploratory objective analyses and the potential confounder list (Table 4) are omitted from the potential risk factors tables (Table 2, Table 3).

Table 2: Potential risk factors for NDD

Mother	Father	Offspring
• Age • Obesity (12 months look back from LMP2) [1] • Smoking (12 months look back from LMP2 and DP) • Substance abuse (12 months look back from LMP2 and DP) • Alcohol abuse (12 months look back from LMP2 and DP) • Schizophrenia, schizotypal and delusional disorders (ever) • Affective Disorder (ever) • Neurotic Disorder (ever) • Rubella (DP) • CMV (DP) • Diabetes (ever) & Gestational Diabetes (DP) • Any concomitant medications associated with valproate-indicated psychiatric conditions (12 months look back from LMP2 and DP) [1] • Any concomitant medications associated with neuropsychiatric adverse effects (12 months look back from LMP2 and DP) [1]	• Substance Abuse (12 months look back from LMP2) • Affective Disorders (excluding bipolar and mania) (ever) • Schizophrenia, schizotypal and delusional disorders (ever) • Neurotic Disorder (ever) • Any concomitant medications associated with valproate-indicated psychiatric conditions (12 months look back from LMP2) [1] • Any concomitant medications associated with neuropsychiatric adverse effects (12 months look back from LMP2) [1]	• Sex • Foetal Alcohol syndrome • Fragile X Syndrome • Congenital CMV • Congenital Rubella • Lejeune/ cri du chat syndrome • Tuberous sclerosis

[1] In addition to recognised risk factors, any co-medications received (including other psychoactive treatments received) during the exposure periods described in section 9.3.1, will be investigated and adjusted for in the analysis using a polypharmacy index.
NDD: Neurodevelopmental disorders; LMP2: Last Menstrual Period + 2 weeks; DP: during pregnancy; CMV: Cytomegalovirus
Omitted from this list are

- risk factors that are exclusion criteria for comparative, sensitivity and exploratory objective analyses:
  - mother: history of epilepsy and NDD,
  - father: history of NDD,
  - child: exposure to AEDs and diagnosis of epilepsy after birth
- paternal factors listed in Table 4.

Table 3: Potential risk factors for CM

Mother	Father	Offspring
• Age • Obesity (12 months look back from LMP2) • Smoking (12 months look back from LMP2 and DP) • Alcohol abuse (12 months look back from LMP2 and DP) • Substance abuse (12 months look back from LMP2 and DP) • Diabetes (ever) • Gestational diabetes (DP) • Rubella (DP) • Varicella (DP) • Toxoplasmosis (DP) • Herpes Simplex virus (DP) • CMV (DP) • Folate deficiency (DP)		• Congenital Rubella • Congenital Varicella • Congenital CMV • Congenital Herpes Syndrome • Congenital toxoplasmosis • Foetal Alcohol Syndrome

CM: Congenital Malformations; LMP2: Last Menstrual Period + 2 weeks; DP: during pregnancy; CMV: Cytomegalovirus

Omitted from this list are

- risk factors that are exclusion criteria for comparative, sensitivity and exploratory objective analyses:
  - mother and father: congenital malformations including chromosomal disorders,
  - mother: teratogenic drugs
- paternal factors listed in Table 4: potential confounders

Table 4: Potential confounding variables by outcome

Outcome	Father
NDD, including ASD	• Age • Bipolar Affective Disorder and mania (ever) • Calendar year of conception of offspring
CM	• Age • Calendar year of conception of offspring

NDD: Neurodevelopmental disorders; ASD: Autism Spectrum Disorder; CM: Congenital Malformations

Paternal age. Multiple epidemiological studies suggest a relationship between advanced paternal age at conception, and adverse neurodevelopmental outcomes (19,20) and congenital malformations (21–23) in offspring. This has been particularly noted with regard to increased risk for autism. 'Paternal Age' will be considered a confounding variable a priori, for both outcomes.

Paternal Bipolar Affective Disorder and Mania. Valproate is indicated in the treatment of epilepsy, mania and migraine (24). Moreover, children of parents diagnosed with mood disorders including mania have been shown to present with increased risk of neurodevelopmental outcomes. For these reasons, in this study, paternal bipolar affective disorder and mania will be considered as potentially confounding the effect of paternal valproate use on the development of neurodevelopmental disorders in offspring.

Maternal epilepsy. There is an increased risk of NDD, including ASD, and CM, in the offspring of female patients with epilepsy (25,26). However the high risk of NDD, including ASD in the offspring of female patients with epilepsy may be due to foetal exposure to AED medication in utero (2), including valproic acid. Offspring from women with epilepsy will only be included in the descriptive analyses of the sample from source population following data extraction, and excluded from the comparative, sensitivity and exploratory objective analyses.

Maternal exposure to AEDs, especially during pregnancy, is known to be a strong risk factor for NDD, including ASD, and CM in offspring (2). Offspring maternally exposed to AEDs (including valproate), *in utero* or three months before conception, will be described and then excluded from the comparative, sensitivity and exploratory objective analyses. Person-time exposed will be classified to take into account intensity of drug exposure during the 3-months pre-conception and pregnancy risk window (see Figure 6 and Figure 7) using the longitudinal K-means clustering (R package kml) algorithm (15) and applied to the relevant analysis. This method allows for a more precise description of exposure of mothers to drugs. More details on the application of the methodology are reported in section 9.3.1.3.

Maternal, paternal and offspring exposure to drugs other than AEDs (including other psychoactive treatments received) during the exposure periods described in section 9.3.1, will be considered using a polypharmacy index.

The plausibility of polypharmacy as a confounding variable or risk factor is based on evidence that polypharmacy is associated with harms including adverse drug effects, drug-to-drug interaction, hospitalization and mortality. Furthermore, there is evidence that psychoactive drugs of other therapeutic class that may often be prescribed in combination with AEDs may be a risk factor for the NDD (such as antidepressants – (6)).

There is currently no consensual definition of polypharmacy. In this study a continuous variable will be defined reflecting medication count as the basis for the exclusive definition of polypharmacy and to describe the medication burden based on the cumulative number of prescribed medications from other therapeutic class (i.e. other than AEDs) to which a relevant individual is exposed within an interval of interest. For the father, this interval would be the 3-months period prior to conception. For the mother the interval would be based on available data on medications prescribed in the three months prior to conception and during gestation period.

Paternal polypharmacy would be a potential confounding variable included in the PS for NDD analysis. Maternal polypharmacy would be considered as a risk factor. For the child, polypharmacy after birth will not be considered as a risk factor in this study. This is because of the high potential of reverse causality; for example there is evidence that children with aberrant behaviours irrespective of diagnosis of NDD are more likely to receive psychotropic polypharmacy. Published literature also suggests subjects with ASD may also have comorbid psychiatric conditions requiring psychotropic treatment and in this regard it is not always possible to define temporality (27–29).

For the CM analysis the polypharmacy score will not be calculated because offspring whose parents were exposed to teratogens (risk factor when considered as maternal exposure and confounders when considered as paternal exposure), associated with maternal exposure in the literature, were already excluded from the CM cohort for the purpose of the comparative analyses (see section 9.3.3.2).

9.3.3.1 Neurodevelopmental disorders, including autism spectrum disorder - additional considerations

Offspring exposure/intake to AEDs and diagnosis of epilepsy. The neurodevelopmental effects of postnatal exposure to AEDs are not completely understood (30). However, AEDs may independently be associated with neuropsychiatric adverse effects (31). Therefore, the main analysis will be restricted to children unexposed to AEDs after birth and with no diagnosis of epilepsy.

Since the potential for reverse causality may apply and since there is likely to be correlation between epilepsy and NDD, exclusion of children receiving AED therapy or with a diagnosis of epilepsy could result in the introduction of selection bias. It is not anticipated that the proportion of children diagnosed with epilepsy and/or receiving AED exposure across the valproate and comparator groups will be differential so the likely impact on the hazard ratio (HR) will be minimal. However, a sensitivity analysis (see section 9.7.5) will be performed to explore the potential impact of having excluded children exposed to AEDs and/or diagnosed with epilepsy as there remains potential suspicion of possibly higher rates of NDD (31), compared to those children without such exposure to the treatment.

9.3.3.2 Congenital malformations - additional considerations

Maternal exposure to teratogenic activity/foetal toxicity. Offspring maternally exposed (three months prior to conception or during pregnancy) to drugs[14] with known teratogenic (32) activity/foetal toxicity (see Annex 3. Additional Information) are at risk of developing the outcomes of interest for reasons other than valproate, i.e. due to intake of other drugs associated with the CM. These offspring will be excluded from the comparative, sensitivity and exploratory objective analyses.

Paternal exposure to teratogenic activity. Paternal exposure to prescription medications, has not been associated with birth defects (3). Nevertheless, offspring from fathers exposed (three months prior to conception[15]) to drugs with known teratogenic (32) activity (based on literature regarding maternal exposure) (see Annex 3. Additional Information) will be excluded from the comparative, sensitivity and exploratory objective analyses.

9.3.3.3 Variables available in data source

A summary description of the variables available for analysis is presented in Annex 3. Additional Information.

9.4 Data Sources

The proposed sources of data are expected to provide a rich set of variables. Given the real-world, retrospective nature of the data, the availability of complete information is expected to vary.

All data elements for this study will be collected from information routinely recorded in the national registries of

[14] In order to account for potential dispensations that can have led to an intake during the 3 months look-back period under investigation, all dispensations that are recorded in the 6 months before conception that gave rise to a teratogenic drug intake during the 3 months prior to conception will be considered.

[15] See footnote 14

- Sweden
- Norway
- Denmark

Databases used in the study are listed in Table 5. Sweden will not be used in the secondary outcome cohort analysis due to lack of paternal linkage to non-live births.

Table 5: Rationale and data source description by country

Country	Data source	Type of data and brief description
Sweden	Multigenerational Register	Source of data for personal identifier for mothers, fathers and offspring, biologic vs adoptive parents, siblings, migration status and marital status. Source of linkage to father (available only for live births).
	Cause of Death Register	Source of data for vital status and further details on diagnosis or cause leading to spontaneous abortions or stillbirths.
	National Prescription registry	Source of data for all outpatient dispensations of prescription medications. Recorded information include data of dispensations, active substance using ATC code, amount sold, pack size and route of administration. Data available since 2005.
	National Patient Registry	Source of data for all diagnosis outcomes of interest in live births. The registry tracks discharge diagnoses with dates and information about procedures. The ICD-10 coding system has been used for the duration of our study period.
	Medical Birth Registry	Source of data for information on gestational age, birth weight, 5-minute Apgar score, live births, stillbirths, smoking during pregnancy, body mass index (BMI), date of conception (estimated from gestational age and date of birth), procedures connected to assisted fertilization.
Norway	Central Person Register	Source of data for personal identifier for mothers, fathers and children, vital status, migration status and marital status.
	Norwegian Prescription Database	Source of data for all outpatient dispensations of prescription medications. Recorded information include data of dispensations, active substance using ATC code, amount sold, pack size and route of administration. Data available since 2004.
	Norwegian Patient Registry	Source of data for all diagnosis outcomes of interest in live births. The registry tracks discharge diagnoses with dates and information about procedures. The ICD-10 coding system has been used for the duration of our study period. Data available for record linkage since 2008.
	Medical Birth Registry	Source of data for information on gestational age, birth weight, 5-minute Apgar score, live births, stillbirths, spontaneous abortions, smoking during pregnancy, body mass index (BMI), date of conception (estimated from gestational age and date of birth), assisted reproductive technology (ART). Source of linkage to father.
	Cause of Death Register	Source of data for vital status and further details on diagnosis or cause leading to spontaneous abortions or stillbirths.

Country	Data source	Type of data and brief description
Denmark	The Danish Civil Registration System	Source of data for personal identifier for mothers, fathers and children, vital status, migration status and marital status.
	Register of Medicinal Product Statistics (RMPS)	Source of data for all dispensations of prescription medications at community pharmacies at individual patient-level. Recorded information include data of dispensations, active substance using ATC code, amount sold, pack size and route of administration. Data available since 1995.
	National Patient Registry	Source of data for all diagnosis outcomes of interest at public and private hospitals (somatic and psychiatric wards). The registry tracks primary and secondary diagnoses with dates and information about procedures and treatment. The ICD-10 coding system has been used for the duration of our study period. Diagnoses at psychiatrists (and other specialists) who have their own private practice are not registered in the National Patient Registry.
	Cause of Death Register	Source of data for further details on diagnosis or cause leading to spontaneous abortions or stillbirths.
	Medical Birth Registry	Source of data for gestational age, birth weight, 5-minute Apgar score, live births, stillbirths, malformations, smoking during pregnancy, body mass index (BMI), date of conception (estimated from gestational age and date of birth). Source of linkage to father.
	The In Vitro Fertilisation Register	The IVF register contains information on IVF treatment carried out at public as well as private fertility clinics in Denmark. For IVF treatments resulting in pregnancy, information on birth, miscarriage or stillbirth is also available.

ATC: Anatomical Therapeutic Chemical; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; IVF: In Vitro Fertilisation

The data sources considered are routinely used for PASS requested by the EMA and the subject of many publications.

9.4.1 Nordic National Registers for Sweden, Norway and Denmark

The availability of national registries makes the Scandinavian countries an optimal choice to identify parent-offspring combinations with linked longitudinal records data. Each individual in Sweden, Norway and Denmark is provided with a unique personal identification number at birth or upon immigration. The personal identification number is used for many administrative purposes, such as an identifier in population and health care registers in all three countries. The number forms the basis for the precise linkage of individual-level data between different registers in Sweden, Norway and Denmark, allowing the creation of a database with individual-level data for any given study. The number also allows family linkage of data.

Sweden, Norway and Denmark have National Patient Registers which contain data from in- and outpatient care. The key variables of the patient registries include diagnosis, surgery and other procedures, as well gender, age, region, hospital, specialty, referrals to/treatment in hospitals or by specialists and hospital admissions/discharges. The National Prescription Registries include all prescribed and dispensed medication to the individual patient covering all pharmacy transactions retrospectively from 1995 (Denmark), 2004 (Norway) and 2005 (Sweden). Country-specific information on the registers is provided below.

Sweden

Individual patient data is collected from both in- and outpatient hospital based specialist care across all of Sweden. The National Patient Register dates back to 1964. From 1987 onward, there is information on all completed inpatient admissions across the country. The collection of outpatient care data began in 2000. The register is updated annually and available from September/October the following year.

All medicines are prescribed electronically in Sweden. The National Prescription Register tracks the full details of all dispensed medications at individual patient-level in Sweden since 01 July 2005. Patients are followed longitudinally through their personal identification number, regardless of which pharmacy they visit. The National Prescription Register is updated monthly and covers all sales of dispensed medication from Swedish pharmacies.

The Medical Birth Register contains information about all pregnancies resulting in delivery in Sweden and is frequently used for quality improvement work and for research. The register contains detailed information about mothers and births. The Swedish Multigeneration Register was established in 1973, and contains information on more than nine million individuals. Data on mothers are available in 97% and on fathers in 95% of index people (those born from 1932 onwards and those alive on 01 January 1961). Individual-level data on breastfeeding is not available in the Swedish registers.

Norway

In Norway, data about live offspring and their parents are obtained from the Medical Birth Registry, the National Population and Housing Censuses (1960-1990), the Central Person Register, and some other national registers. The database is completely anonymous, in that the 11-digit national identity number has been removed and substituted by another number with no connection to the original number. Thus, it is not possible to connect to micro data from sources outside the database. To further prevent the identification of the individual, parts are replaced with information about birth and home municipality/county. The Medical Birth Registry of Norway holds information on all pregnancies and births since 1967 (notification is compulsory) from 12 completed weeks of gestation onwards. Linkage to fathers is available for 97% of live and non-live births (3). Individual-level data on breastfeeding may not be available in the Norwegian registers.

Denmark

Denmark has the longest-standing civil registration system in the world. From 1968 and onwards, the Danish Civil Registration System (CPR) has held information on all persons with a permanent address in Denmark, and the relations between spouses, parents and offspring. Therefore, there is considerable scope for creating a multigenerational database that can accommodate multiple research purposes. The National Patient Register holds good quality data on diagnoses of childhood NDD and adults with psychiatric disorders in secondary care. The Danish Medical Birth Register has held near complete information on pregnancy (live and non-live births) and birth details for mothers and offspring respectively since 1973, from 22 completed weeks of gestation onwards. Data on fathers are available for 97.5% of live births (6). Information on breastfeeding is available from 2012 in the Danish registers.

9.5 Study Size

The primary objective of this observational study is to explore the association of risk of NDD, including ASD in offspring paternally exposed to valproate.

The trend in the prevalence of developmental disabilities in US children aged 3-17 has been reported to be 13.9% between 1997-2008 (33). While there is a prevalence of approximately 1% total population for ASD globally, developmental intellectual disability ranges from 0.4 to 3% globally. According to a large population-based case-control study (34) using Danish registry data, 3.7% of children aged up to and including 5 years in the control group (unexposed to AEDs) had learning disabilities (defined as mental retardation (ICD-10: F7x), specific developmental disorders (ICD-10: F80–83), ASD (ICD-10: F84), emotional/behavioural disorders (ICD-10: F9x) or having special educational needs). Therefore it is reasonable to assume a background risk in the range of 3-4% for NDD in live offspring.

In this study, the primary endpoint is NDD, including ASD. Given the interest in ASD, the sample size will be estimated for this endpoint, with the assumption that this endpoint is nested within the primary endpoint. Accordingly, the sample size should be sufficient to observe the desired effect size for the composite primary endpoint.

As previously reported, maternal use of valproate during pregnancy is associated with significantly increased risk of ASD (2). According to the observational study conducted in live offspring within Denmark using registry data, risk of ASD after 14 years of follow-up has been estimated to be 1.53% (95% Confidence Interval (CI) 1.47,1.55). In the same study the corresponding risk of ASD in live offspring exposed maternally to valproate has been estimated to be 4.42% (95%CI 2.59, 7.46). The adjusted HR was 2.9 (95%CI 1.7, 4.9). Data from an observational population-based cohort study on risk of ASD in live offspring following paternal use of SSRIs before conception (7), using Nordic registry data, reported an incidence of 1.13% of ASD in live offspring born to fathers who had redeemed a prescription for SSRIs in the last 3 months prior to conception. The incidence rate was 169 per 100,000 person-years. In an unexposed comparator group (no paternal exposure to SSRI) the corresponding incidence rate was 110 per 100,000 person-years. Thus, the incidence rate in the exposed cohort corresponded to a 54% increased risk. After adjustment for potential confounders the HR was 1.43 (95%CI 1.18-1.74).

Using this information the following assumptions will be made for sample size estimation for the ASD endpoint:

- The background incidence of interest will focus on the incidence of ASD in young offspring since this is an outcome of interest within the composite endpoint of NDD. This is assumed to be 1.5%.
- An effect size based on ratio of rates that ranges between 1.5 to 3.0.
- Total births for study period: Norway 2004-2017 n=~0.8M; Denmark 1995-2017 n=~1.3M, and Sweden 2005-2017 n=~1.5M
- Record linkage for family unit of minimum of 95% all births across all countries (6)
- Incidence rate of valproate monotherapy in adults of 1.2/1000 patients (35)
- Incidence of AED therapy and/or diagnosis in children of 0.15%[16] (36)

[16] Based on Swedish national population statistics where the population in this age group is calculated to be 10,117,269 (http://www.statistikdatabasen.scb.se) the incidence of initiation in this age group is 0.1%. Since it is possible that children with some forms of epilepsy may not receive AEDs a conservative adjustment of 50% will be made to this incidence estimate such that the period incidence of 0.15% in children aged 0-11 years inclusive,

The minimum desirable sample size should be able to estimate such an effect with an appropriate margin of error. Such uncertainty in the findings will be quantified by calculating a 95% CI around the observed effect measures (HR). CI width will provide an indication of precisions of the point estimate; the upper and lower limit will provide a range of credible values consistent with observed data. Since this study is exploratory and the risk of the outcome in offspring paternally exposed to either valproate (monotherapy) or lamotrigine/levetiracetam (monotherapy remains to be defined, the following sample size calculations presented in Table 6 use a range of effect sizes based around the aforementioned estimates for analogous drug-event associations.

Table 6: Expected sample sizes to estimate various effect size given different reference risks of ASD in offspring paternally exposed to other AEDs (by power: 90% and 80%)

Reference Risk of ASD	Effect size											
	1.5	2	2.5	3	3.5	4	1.5	2	2.5	3	3.5	4
	Power: 90%						Power: 80%					
0.5%	42948	12970	6718	4302	3082	2364	32482	9888	5154	3316	2384	1836
1.0%	21346	6440	3334	2132	1526	1170	16144	4910	2558	1644	1182	910
1.5%	14144	4264	2204	1410	1008	772	10700	3252	1692	1088	780	600
2.0%	10544	3176	1640	1048	748	574	7976	2422	1260	808	580	446
3.0%	6944	2086	1076	686	490	374	5254	1592	826	530	380	292
4.0%	5144	1542	794	506	360	274	3892	1178	610	390	280	214

ASD: Autism Spectrum Disorder.

For the ASD endpoint, it is assumed that the risk of ASD in the reference group (live offspring paternally exposed to lamotrigine/levetiracetam monotherapy) is 1.5%. In order to be able to observe a HR of 2.0 (i.e. doubling of risk in offspring paternally exposed to valproate) with 5% significance and 80% power, a sample size of 3253 children within the family linked unit would be needed across all three countries. This requires a minimum of 1627 offspring within a family linked unit with paternal exposure to valproate (monotherapy), and a minimum of 1627 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (monotherapy).

For the primary endpoint, the same assumptions exist with the exception that the assumed risk of NDD (including ASD) in the reference group is 4%. Therefore, in order to be able to observe a HR of 2.0 (i.e. doubling of risk in offspring paternally exposed to valproate) with 5% significance and 80% power, a sample size of 1178 offspring within the family linked unit would be needed across all three countries. This requires a minimum of 589 offspring within a family linked unit with paternal exposure to valproate (monotherapy), and a minimum of 589 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (monotherapy).

The eligible study cohort sizes are projected as follows:

diagnosed with epilepsy and/or treated with AEDs can be used for sample size assumptions. Furthermore, since a literature review reveals no equivalent estimates in Norway and Denmark, this estimate will be applied to Norway and Sweden to adjust feasibility counts.

Based on the aforementioned birth rate statistics and an assumption of 95% of births linked to fathers, an incidence rate of valproate monotherapy of 1.2/1000 patients and an incidence of 0.15% for childhood exposure to AEDs and/or diagnosis of epilepsy, we estimate an eligible population of offspring within a linked family unit with paternal valproate exposure of n=~940 between 2004-2017 for Norway, n=~1495 between 1995-2017 for Denmark, and n=~1645 between 2005-2017 for Sweden. The estimated pooled eligible family linked offspring cohort for valproate monotherapy is 4,080 across all three countries.

If these projections are observed, this study should have a sufficient number of paternally exposed valproate offspring within each country to observe a HR of 2.0 for the primary endpoint of NDD, including ASD, with 5% significance and 80% power. It is also anticipated that this study would have a sufficient number of paternally exposed valproate offspring across all three countries to observe a HR of 2.0 for the endpoint of ASD (see sensitivity analysis section 9.7.5)

In accordance with our proposal, the comparative evaluation of CM as a composite outcome will be secondary and therefore sample size estimation does not apply. For completeness an evaluation of the study power for a comparative evaluation based on major CM (since these comprise the smallest subgroup of CM but most serious) is presented below, with the assumption that this outcome is nested within the secondary composite outcome. Accordingly, the sample size should also be sufficient to observe the desired effect size for the comparative analysis of the composite secondary endpoint for Norway and Denmark.

The background incidence of major CM in pregnancies has been estimated to be 37.1 cases per 1000 pregnancies among live births (up to 1 year of age) or stillbirths (37). The combined incidence estimate of major CM associated with maternal valproate exposure (spina bifida, ventricular septal defect, atrial septal defect, cleft palate, hypospadias (boys only) and polydactyly) is 56.6 cases per 1000 pregnancies (17). It is acknowledged that this estimate does not contain all major CM and is therefore an estimate. According to the systematic review by Jentink et al. of 8 studies which explore the risk of major CM associated with valproate exposure in the first trimester compared to other AED, the effect size ranged from OR 2.9 (05% CI 1.1-7.7) for cleft palate to OR 5.5 (95%CI 1.4-25.4) for polydactyly; with the strongest association reported for hypospadias in boys (OR 6.6 (95%CI 2.8-16.6)), although the CI were wide reflecting the small numbers analysed. It would be reasonable to select the smallest effect size in the smallest subgroup of CM (i.e. major) to explore the power of this study to reject the null hypothesis of no difference. Assuming a minimum effect size of 2.5, where the background incidence was 3%, with 80% power, a study with a total sample size of 826 family linked offspring (n=413) in the valproate monotherapy group and n=413 in the comparator monotherapy group would be desirable.

For Denmark and Norway, linkage is feasible for approx. 97% for live births, but completeness decreases for non-live births. Assuming a worst case scenario of 50% of pregnancies with record linkage, it is anticipated that ~720,000 family linked offspring would be observed for Norway and ~660,000 for Denmark. The corresponding estimates of family linked offspring with paternal exposure to valproate monotherapy would be ~860 and ~790 respectively. Assuming a similar number of family linked offspring with paternal exposure to the composite monotherapy reference AED group are available to achieve a total cohort size of ~1720 for Norway and 1580 for Denmark, these numbers would be more than sufficient to permit the observation of the aforementioned effect size of 2.5 for major CM assuming a background risk of 3%, with 80% power.

Since the paternal record linkage for pregnancies with outcomes reported prior to birth is not feasible for Sweden all relevant CM analysis are presented separately

9.6 Data Management

9.6.1 Statistical analysis

Statistical analyses will be performed using statistical packages (Statistical Analysis System [SAS], STATA and R [version 3.1.1, or above]) and will be described in detail in the Statistical Analysis Plan (SAP).

9.6.2 Database management

The processes for database management differ by country. Generally, the data is stored at the database level and analysed in accordance with local policy. SAS or R language (version 3.1.1, or above) will be utilized for access to the raw data, to manage the analytic datasets and to conduct data analysis. If the study is conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures. This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation (ICH) guidelines for data management.

9.7 Data Analyses

9.7.1 General considerations

The distribution of each variable will be examined graphically using boxplots, symmetry plots, normal quantile plots and normal probability plots. Exploratory analyses to provide insight into general patterns will be conducted using number and percent within each category for categorical variables, and mean (standard deviation, SD), median (interquartile range, IQR), and other relevant summary statistics for continuous variables. Where appropriate, a log transformation of continuous variables will be applied to handle skewness (back-transformed prior to reporting) or a non-parametric approach will be adopted if there is no appropriate transformation. Quantitative variables may be categorised into quartiles as required. To identify outlying values of variables, such as gestational age and weight, the Cook's distance will be calculated for each offspring after model fitting. The Cook's distance measures the change in fitted values with and without the presence of each offspring, i.e. the impact of each offspring on the fitted values. Offspring that have a Cook's distance greater than four times the mean will be classified as influential[17]. For influential offspring it is likely that variables had extreme values. If extreme values (outliers or leverage points[18]) are observed, they will be assumed as missing and excluded from the final model.

The descriptive (section 9.7.2), and comparative (section 9.7.3.2) analyses will be undertaken by country. For analysis of the primary outcome, data will then be pooled across the three countries, via a meta-analytic approach (see section 9.7.6). For analysis of the secondary outcome, data will be pooled across Norway and Denmark only via a meta-analytic approach

[17] A data point is influential if it unduly influences any part of a regression analysis, such as the predicted responses, the estimated slope coefficients, or the hypothesis test results.

[18] Outliers and high leverage data points have the potential to be influential, but generally further investigations are needed to determine whether or not they are actually influential.

(see section 9.7.6). In addition, the case assessment will also be presented by country (see section 9.3.2.3). Table 7 shows the analyses presented in Section 9.7 by study outcome.

The populations at study will include each individual offspring (or non-live birth) as the unit for analysis, therefore if the mother and father have more than one offspring they can be included more than once in the study; each offspring/non-live birth will coincide with the linked triple offspring/non-live birth, mother and father. Furthermore all variables collected for fathers and mothers will be re-calculated for each pregnancy.

Table 7: Analyses for study objectives, by Data Analysis section

Sub-section		Cohort	
Section number	**Analysis description**	**NDD**	**CM**
9.7.2.1	Cohort characteristics	x	x
9.7.2.2	Cumulative incidence proportion, rate and time to event	x	x[1]
9.7.3.1	Univariate Analyses	x	x
9.7.3.2.1	Effect estimation - NDD, including ASD	x	
9.7.3.2.2	Effect estimation – CM		x
9.7.3.2.3	Propensity score	x	x
9.7.6	Meta-analysis	x	x
9.7.4	Exploratory objective analyses	x	x
9.7.5	Sensitivity analyses	x	x
9.7.6	Missing data analysis	x	x

NDD: Neurodevelopmental Disorders; ASD: Autism Spectrum Disorder; CM: Congenital Malformations
1 - for CM only cumulative incidence proportion will be calculated.

9.7.2 Descriptive Analyses

9.7.2.1 Cohort characteristics

Demographic characteristics of mother, father and offspring will be presented for both *the primary and secondary outcome cohort* and separately for *paternal exposure groups* (valproate and lamotrigine/levetiracetam (composite and separately) in monotherapy). Other characteristics (e.g. age at first diagnosis of outcome) and other co-existing risk factors for primary and secondary outcomes of interest (e.g. medication use within 3 months prior to LMP2 (paternal and maternal) and during pregnancy (maternal)), and concurrent relevant morbidities according to each relevant index date, will also be summarised. Thus, contingency tables reporting the characteristics of offspring with NDD, including ASD, as well as outcomes of CM occurrence by paternal and maternal exposure groups, will be provided. Summary description of the frequency of extremely low birth weight, very preterm and extremely preterm newborns will be provided for the primary outcome cohort, by paternal and maternal exposure group (a sensitivity analysis will be performed excluding preterm and low birth weight offspring, section 9.7.5). Summary description of the frequency of children exposed to AEDs

and/or diagnosed with epilepsy after birth will be provided (a sensitivity analysis will be performed including those children, section 9.7.5). Summary description of the frequency of stillbirth, spontaneous abortion, intrauterine growth retardation and perinatal mortality, associated to a diagnosis of CM, will be also provided. Data will also be stratified by age and calendar period. A descriptive table of the frequency of fathers who switch to or switch from an AED other than valproate, lamotrigine or levetiracetam, even if on monotherapy, will be provided. A descriptive table with a summary of the case assessments (see section 9.3.2.3), undertaken by study clinical investigators using the registry data on a random sample of cases, will be provided at aggregate level.

A STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) diagram will be provided to show exclusions to be applied in order to create cohorts for analysis.

9.7.2.2 Incidence examination

The cumulative incidence proportion, rate and time to onset of NDD, including ASD will be calculated as well as cumulative incidence proportion for composite CM endpoint and specific CM target body system organ groups based on ICD-10 codes. These statistics will be presented for each overall cohort and separately for offspring *paternally exposed to valproate or lamotrigine/ levetiracetam (composite and separately) in monotherapy* 3 months prior to LMP2.

The cumulative incidence (risk) of the primary outcomes reported each year will be explored by estimating the cumulative incidence of incident reports (plus 95% CI). For purposes of this analysis the denominator is defined according to the population initially at risk at the beginning of the study, since the estimates are cumulative; that is live births for NDD, including ASD and live plus non-live births for CM. The numerator will comprise of counts of incident events as recorded during each year and summed to reflect the cumulative count for all years up to that point. The cumulative incidence proportion will be calculated according to the formula:

(Total number of offspring paternally exposed with newly diagnosed outcome during each cumulative year of interest /Population initially at risk) x 100

For each exposure group, the numerator for each year will contain the number of offspring for whom the incident outcome has been recorded in that year and will exclude offspring who have had an outcome previously, within the study period. The denominator will include offspring within the numerator and also offspring who did not have an outcome recorded in the current year or preceding years (i.e. only the ‘at risk’ population will be considered).

The cumulative incidence rate of the primary outcome will be modelled using survival methods and expressed as number of cases per 1000 patients-years at risk (+95%CI). Data may also be stratified according to other relevant strong risk factors for events of interest (age, gender) and stratum-specific incidence rates examined.

For the time to event analysis of the primary outcome, a semi-parametric Proportional Hazards (PH) regression model will be derived to describe the time to event, which will be presented graphically. At least 10 cases will be required per event for crude estimates. A smoothed estimate of empirical hazard function will also be plotted using an epanechnikov kernel (bandwidth to be determined empirically from data). These will be used to describe how the baseline risk of an event changes over time.

In addition, cumulative incidence proportions for the entire period, 0-12 years for Denmark and Sweden and 0-10 years for Norway, will also be presented; this will be calculated as the

total number of offspring experiencing the outcome (NDD and CM, separately) during the entire follow-up (i.e. the sum of the number of events for the years 0 to 12 for Denmark and Sweden, and 0 to 10 for Norway) divided by the initial number of offspring included at the start of follow-up (i.e., population used in the analysis). Furthermore considering index date in the CM cohort will start before or on date of birth and that patients will be followed up until 12 years of age at maximum (10 years of age for Norway), there will be patients with a follow-up longer than 12 years (10 years for Norway), and therefore cumulative incidence proportion for the entire follow-up will include a longer period than 12 years for Denmark and Sweden (but shorter than 13 years). For Norway, the cumulative incidence proportion for the entire follow-up will include a longer period than 10 years, but shorter than 11 years.

9.7.3 Comparative analyses

The following relates to primary and secondary objectives. These analyses will be conducted on the cohort to evaluate the effect of valproate on NDD, including ASD (see cohort definition in section 9.2.2 and 9.2.2.1) and on the cohort to evaluate the effect on CM (see cohort definition in section 9.2.2 and 9.2.2.2). Fathers who switch to or switch from an AED other than valproate, lamotrigine or levetiracetam, even if on monotherapy, will be excluded from the comparative analyses (as reported in section 9.3.1) (further details are provided in the multivariate analysis section 9.7.3.2).

For the *comparative analyses*, offspring maternally exposed to AEDs (including valproate, lamotrigine and levetiracetam) *in utero,* or during 3 months prior conception, as well as offspring from a mother with a history of epilepsy, will be excluded. For the *comparative analyses related to the primary outcome*, offspring exposed to AEDs and/ or diagnosed with epilepsy after birth will be excluded.

9.7.3.1 Univariate analyses

Univariate analysis for each cohort will be performed to characterise exposure groups (valproate and lamotrigine/levetiracetam (composite and separately) in monotherapy) with respect to potential covariates. Additionally, univariate analysis will be used to assess the strength of the relationship of any potential confounders to the primary (NDD including ASD) and secondary (CM) outcomes. Differences between categorical variables will be tested using Fischer's Exact test OR Chi-squared test (depending on event counts), and differences between continuous variables will be tested by using parametric two sample t-tests, where appropriate. All risk and incidence estimates will be reported with a 95% CI. Significance level will be set to $p<0.05$ using 2-sided testing.

9.7.3.2 Multivariate analysis

The *primary analysis* will be conducted to investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy) compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception. All the analyses on NDD, including ASD, will only draw conclusions about NDD, including ASD, as a composite outcome, however a sensitivity analysis will focus on ASD alone (section 9.7.5).

The *secondary analysis* will be conducted to investigate the risk of CM in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.

9.7.3.2.1 Effect estimation - Neurodevelopmental disorders, including autism

A crude and a propensity-score (PS) weighted (section 9.7.3.2.3) Cox PH regression model will be used to estimate the HR of NDD, including ASD, with 95% CI (using offspring's calendar age in years as the underlying timescale) in offspring paternally exposed to valproate monotherapy within 3 months prior to LMP2 date compared to the reference group comprised of offspring paternally exposed to lamotrigine or levetiracetam (composite monotherapy) in the same time period. Inclusion of covariates not retained in the PS (section 9.7.3.2.2), in the Cox PH model will be considered in the event of imbalance in prognostically important variables. Covariates measured after index date will be included as time dependent in the Cox PH model, as appropriate. Post-estimation model diagnostics will be undertaken for each final parsimonious model, including log-log plots and Schoenfeld residuals, to assess the proportionality assumption.

Multiple offspring per father is possible and will introduce within-family dependencies into the data. Therefore in the analyses, paternal clustering will be taken into account by correcting standard errors with sandwich estimators (38). For purposes of the primary objective analysis for which the study is powered, a first Cox PH model will be estimated irrespective of clusters classification (section 9.3.1.3). This approach has the limitation to ignore intensity of exposure in the two exposure groups. To overcome this limitation, the first model will be repeated including the exposure intensity variable (estimated based on clusters as by application of k-means methodology (section 9.3.1.3)) as an effect modifier, i.e. the interaction exposure*k-means will be included in the model. This second approach has the advantage of providing an estimate of the effect of paternal exposure to valproate vs the comparator group stratified by exposure intensity as measured by the k-means clusters.

9.7.3.2.2 Effect estimation – Congenital malformations

A crude and a PS-weighted (section 9.7.3.2.3) logistic regression model will be used to estimate the Odds Ratios (OR) of CM with 95% CI in offspring paternally exposed to valproate monotherapy within 3 months prior to LMP2 date compared to the reference group comprised of offspring paternally exposed to lamotrigine or levetiracetam (composite monotherapy) in the same time period. Inclusion of covariates not retained in the PS (section 9.7.3.2.2) will be considered in the logistic model in the event of imbalance in prognostically important variables.

Multiple offspring per father is possible and will introduce within-family dependencies into the data. Therefore in the analyses, paternal clustering will be taken into account by correcting standard errors with sandwich estimators (38).

For purposes of the secondary objective analysis, a first logistic model will be performed irrespective of clusters classification (section 9.3.1.3). A second logistic model will be performed including the exposure intensity variable (estimated based clusters as by application of klmeans methodology) (section 9.3.1.3), as an effect modifier, i.e. the interaction exposure*k-means will be included in the model. Advantages and disadvantages of these approaches are reported in section 9.7.3.2.1.

9.7.3.2.3 Propensity-score

Separate PS models will be constructed for the primary and secondary analyses. The PS will reflect the probability of an offspring being assigned to valproate or the comparator exposure group (lamotrigine/levetiracetam), given a set of observed covariates (these being different for the primary and secondary analyses). These PS will then be used to equate the groups of offspring paternally exposed to valproate with offspring paternally exposed to lamotrigine/levetiracetam based on observed covariates.

The process is as follows: All potential confounders (section 9.3.3), as reported in literature, will be considered for inclusion in each PS model (39). Also, variables that are unrelated to the exposure but related to the outcome (section 9.3.3) will be included in the PS model. The inclusion of these variables will increase the precision of the estimated exposure effect without increasing bias. In contrast, including variables that are related to the exposure but not the outcome can decrease the precision of the estimated exposure effect without decreasing bias (39). Candidate covariates will be considered to enter the model if the OR or relative risk in a single association with the outcome is higher than 1.1 or lower than 0.9. In order to model the PS for the analysis of each of the two outcomes, three model approaches will be used and compared. The first approach will consist of a logistic regression model with all potential confounders associated with the outcome. Continuous covariates will be modelled using restricted cubic splines as they not only allow for non-linearity, but are also associated with superior model fit at the tails of distributions (40). An attempt to prevent overfitting will be made by specifying 4 knots at 5, 35, 65 and 95% based on Harrell's recommended percentiles (41). Additionally, two-way interactions will be included only for variables which have been identified by a clinician as clinically meaningful. The second modelling approach will be the use of a random decision forest model (42). The advantage of this approach is that interactions between covariates are by definition incorporated into the model and strong predictors and interactions can thus be identified. The random forest model extends easily to multiple outcomes. Finally, the third modelling approach will be a logistic regression informed by the random forest model. In this approach, data-driven identification of interactions as identified by the random forest model will be incorporated into the logistic regression model.

Once the propensity scores are estimated (separately for the primary and secondary outcome cohorts) they will then be used as weights in the inverse probability of treatment weights approach to balance differences in covariate distribution between offspring paternally exposed to valproate and offspring paternally exposed to lamotrigine/levetiracetam in the adjusted analyses. PS weighting will be used instead of matching for increased generalisability and to avoid the exclusion of patients from the adjusted analyses due to lack of matches (43–46); this is deemed as particularly important in situations where the outcome of interest is relatively rare or infrequent.

For each PS model, the distributions of estimated propensity scores will be visually compared across the three models, separately for the primary and secondary outcome. Selection of the best models for the primary and secondary outcome cohorts will be based on the balance achieved in the weighted exposure groups after using inverse probability of treatment weights. Only the best PS models for the primary and secondary outcome cohorts will then be used to apply inverse probability of treatment weights in the multivariate analysis.

The best PS modelling approach might not be the same for the two cohorts, and similarly the covariates included in the PS model will differ as the two outcomes have different risk factors and confounders.

A sensitivity analysis to compare the results from the PS-weighted approach with the traditional approach of covariate adjustment will be performed, as reported in section 9.7.5, for both primary and secondary composite outcomes, using the composite lamotrigine/levetiracetam monotherapy comparator.

9.7.4 Exploratory objective analyses

For the *exploratory analyses*, offspring maternally exposed to AEDs (including valproate, lamotrigine and levetiracetam) *in utero,* or during 3 months prior conception, as well as offspring from a mother with a history of epilepsy, will be excluded. For the *exploratory analyses related to the primary outcome*, offspring exposed to AEDs and/or diagnosed with epilepsy after birth will be excluded.

For exploratory objective 5, for offspring paternally exposed to AED polytherapy, summary cohort characteristics and univariate analysis (section 9.7.3.1) will be performed to describe the putative risk factors and frequency of of the primary composite outcome (NDD, including ASD) and for the secondary composite outcome (CM) for offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine and levetiracetam) and offspring paternally exposed to levetiracetam/lamotrigine in polytherapy (i.e. polytherapy including at least one of them, and excluding valproate) at the time of conception.

For exploratory objective 6, to explore potential for unmeasured family-related confounding factors (such as genetic liability for neuropsychiatric conditions or congenital malformations and early postnatal environmental influences), an exploratory sibling-matched descriptive analyses will be conducted, separately, on the primary composite outcome (NDD, including ASD) and the secondary composite outcome (CM) whereby only families with paternal valproate exposure-discordant siblings will be included (at least one offspring with paternal valproate exposure and one offspring without exposure). For this analysis, summary cohort characteristics and univariate analysis (section 9.7.3.1) will be performed to describe the subgroups and identify potential risk factors for the composite primary and secondary outcomes of interest, respectively.

For exploratory objective 7, which is to investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception in Sweden, the descriptive (section 9.7.2), and comparative (section 9.7.3.2) analyses will be presented separately. This is because the population for analysis is comprised of live births only and therefore is systematically different to the cohorts for CM analysis in Norway and Denmark

For exploratory objective 8, on the basis of lack of knowledge of the likely pattern of CM in offspring paternally exposed to valproate, it is of interest to describe the spectrum CMs according to the body system organ class affected from the malformation (see classification in section 9.3.2.2). Therefore, an exploratory objective is proposed to describe the spectrum of sub-types by organ class, with stratification as major or minor CM where feasible.

9.7.5 Sensitivity analyses

The following sensitivity analysis will be conducted:

1. *Variation of exposure time window for primary outcome:* Examine the association between extended risk window of paternal valproate exposure (6 months) and NDD, including ASD, in the offspring to investigate if there is an effect of valproate exposure other than through the spermatogenic cycle.
2. *Outcome of interest restricted to ASD specifically (ignoring all other NDD diagnoses)*: Investigate the risk of ASD in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception.
3. *Exclusion of offspring with a birth weight lower than 1000gr or born prior to 8th month of pregnancy, for primary outcome.* There are suggestions for evidence of association between preterm birth/low birth weight and NDD (47–49). If AEDs affect preterm birth and preterm birth affects NDD, this means that preterm birth could act as a mediator between AEDs and NDD. In the same way, if AEDs affect very low birth weight and very low birth weight affects NDD, this means that very low birth weight could act as a mediator between AEDs and NDD. Adjusting for a mediator introduces a bias, therefore this sensitivity analysis will be performed excluding extremely low birth weight, very preterm and extremely preterm newborns to explore the potential impact introduced by inclusion of this sub-population of offspring on the point estimate.
4. *Handling of missing diagnoses for CM outcome*: Since a lot of diagnoses/reasons for spontaneous abortions and stillbirth could be missing, due to under-reporting, a sensitivity analysis will be performed to investigate the risk of CM using a broader definition of the outcome. It will include all the ICD-10 codes of interest where available, as reported in section 9.3.2.2, for live births and spontaneous abortions/stillbirths as well as all spontaneous abortions/stillbirths without an ICD-10 code for the diagnosis/reason. The main advantage of this broader definition of the outcome would allow to include in the analysis under reported cases of CM, on the other hand missing diagnoses related to cases different from CM could be included.
5. *Simple pairwise comparison valproate vs lamotrigine and valproate vs levetiracetam in monotherapy.* Valproate, lamotrigine and levetiracetam are medications with similar indications but that may be systematically prescribed for different type of epilepsy (such as valproate for genetically determined epilepsy and lamotrigine for focal onset epilepsy) and potentially other indications (lamotrigine might be prescribed for bipolar disorder and levetiracetam is not). Moreover, they were licensed in different periods (levetiracetam since 2000; lamotrigine since early 1990s; and valproate since 1967 to

treat epilepsy and since 1995 to treat bipolar disorder) resulting in systematic different in the treated populations. With the objective to evaluate if there is a differential effect of using one or the other comparator, a supplementary analysis will be provided to contrast valproate paternal exposure to separately lamotrigine and levetiracetam paternal exposure for the purpose of both NDD and CM outcome:

a. Describe the characteristics of mother, father and offspring for both the primary and secondary outcome cohort and separately for paternal monotherapy exposure to individual AEDs (valproate or lamotrigine or levetiracetam).
b. Investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine (monotherapy) treatment at the time of conception.
c. Investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to levetiracetam (monotherapy) treatment at the time of conception.
d. Investigate the risk of CM, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine (monotherapy) treatment at the time of conception, in Norway and Denmark only.
e. Investigate the risk of CM, in offspring paternally exposed to valproate (monotherapy), compared to levetiracetam (monotherapy) treatment at the time of conception, in Norway and Denmark only.

6. *Comparison of the PS-weighted model with the traditional covariate adjustment model:* A Cox PH regression model will be used to estimate the HR of NDD, including ASD, with 95% CI (using offspring's calendar age in years as the underlying timescale) in offspring paternally exposed to valproate monotherapy within 3 months prior to LMP2 date compared to the reference group comprised of offspring paternally exposed to lamotrigine or levetiracetam (composite monotherapy) in the same time period. A logistic regression model will be used to estimate the OR of CM with 95% CI in offspring paternally exposed to valproate monotherapy within 3 months prior to LMP2 date compared to the reference group comprised of offspring paternally exposed to lamotrigine or levetiracetam (composite monotherapy) in the same time period. The list of confounders to be included is reported in Table 4. Within-family dependencies introduced by multiple offspring per father will be accounted for using sandwich estimators. Different results are expected because two different set of variables will be used for the adjustment due to the inclusion of risk factors in the PS model to improve efficiency; (c) noncollapsibility of the two models (46,50–52) ("the conditional OR or HR does not equal the marginal OR or HR in the presence of non-null treatment effect, even in the absence of confounding and effect modification" (52)).
7. *Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy.* As reported in section 9.3.3.1 the neurodevelopmental effects of postnatal exposure to AEDs and/or diagnosis of epilepsy on risk of NDD are not completely understood. Therefore, in the primary analysis such children are excluded. A sensitivity analysis will be conducted to explore the impact on the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine or levetiracetam (composite monotherapy) treatment at the time of conception will be performed by including these offspring. Offspring exposure to AEDs and diagnosis of epilepsy between birth and the exit date will each be considered time dependent, and thus allowed to take place at any time during the follow-up period. However, after the first dispensation of AEDs, the offspring will be considered exposed until the exit date.

8. *Validation of the assumption that individuals are exposed to one DDD per day.* WHO DDD is the assumed average maintenance dose per day for a drug used for its main indication (i.e. epilepsy for valproate, lamotrigine and levetiracetam) in adults. This does not necessarily reflect the recommended or Prescribed Daily Dose. Therapeutic doses for individual patients and patient groups will often differ from the DDD as they will be based on individual characteristics (such as indication, age, weight, ethnic differences, type and severity of disease) and pharmacokinetic considerations. A comparison (ratio) between the distribution of estimated treatment durations (expected) and time between prescriptions (observed) will be provided with the caveat that this will necessarily be affected by the DDD methodology approximation. In order to partially overcome this limitation, this comparison will be provided separately for patients with and without an indication of epilepsy, as epilepsy is the main indication for the medicines at study therefore the indication used by WHO to estimate DDD. It is expected that the use of WHO DDD will be a better approximation of the observed treatment duration among patients with a diagnosis of epilepsy, with a ratio closer to one than for other indications. The distribution of estimated treatment durations (expected) will be compared to the distribution of time between prescriptions (observed), *separately for lamotrigine, levetiracetam, valproate and for patients with and without an indication for epilepsy*, using the following formulas:

   Observed time between prescriptions for patient i is

$$\sum_{j=1}^{k-1} days\left(prescription_{j+1} - prescription_j\right)$$

   where k is the number of prescriptions for each patient.

   Expected treatment duration for patient i is

$$\frac{\sum_{j=1}^{k-1} n.\ pkg\ in\ prescription_j * n.\ dosage\ unit\ in\ each\ pkg}{WHO\ DDD}$$

   where k is the number of prescriptions for each patient.

   The ratio of Observed over Expected for patient i is

$$\sum_{j=1}^{k-1} days\left(prescription_{j+1} - prescription_j\right) \Big/ \frac{\sum_{j=1}^{k-1} n.\ pkg\ in\ prescription_j * n.\ dosage\ unit\ in\ each\ pkg}{WHO\ DDD} =$$

$$= \sum_{j=1}^{k-1} \frac{days\left(prescription_{j+1} - prescription_j\right) * WHO\ DDD}{n.\ pkg\ in\ prescription_j * n.\ dosage\ unit\ in\ each\ pkg}$$

   The ratio for the population

$$\sum_{i=1}^{n} \left(\sum_{j=1}^{k-1} \frac{days\left(prescription_{j+1} - prescription_j\right) * WHO\ DDD}{n.\ pkg\ in\ prescription_j * n.\ dosage\ unit\ in\ each\ pkg} \right) / n$$

   where n is the number of patients and k is the number of prescriptions per patient.

   Under the assumption of perfect compliance of each patient, if the Ratio for the overall population is between 0.8 and 1.2 then the WHO DDD is a good approximation of the reality; the more the ratio departs from the good approximation range the more the real daily dose prescribed diverge from the WHO defined daily dose. It is expected to have a good approximation to the reality for patients with the epilepsy indication for AEDs.

This measure will be affected both from the approximation of using the WHO DDD and the compliance of patients to the treatment. The less the compliance, the more the ratio departs from good approximation (0.8-1.2). Since the dose prescribed is not available, it will not be possible to assess what affected more the results.

Sensitivity analysis 8 will be performed only in the Primary Outcome Cohort for Descriptive Analyses

9. *Narrow case definition for secondary outcome - focus on CM in live births*: Since the population for analysis of the secondary outcome for Sweden is comprised of live births, the distribution of CM observed in this population is likely to reflect functional defects and minor morphological abnormalities, rather than major morphological abnormalities (usually associated with fatal outcome during gestation). A sensitivity analysis will therefore be performed on the corresponding live birth population for Norway and Denmark to describe the corresponding risk and underlying distribution of CM associated with live births.
10. *Continuous measure of cumulative exposure*: Investigate separately the risk of NDD, including ASD, as well as CM, in offspring paternally exposed to monotherapy treatment with valproate, lamotrigine or levetiracetam at the time of conception, using cumulative exposure to treatment. Cumulative exposure will be calculated as the total amount of DDD intake that a father is exposed to over the 3-months time window prior to LMP2 date, i.e. the sum of the DDD in all 14-day intervals as reported in Figure 8.
    a. In order to account for potential differences in the association between the cumulative exposure and the outcome at study between different treatments, an interaction term of the continuous variable representing the cumulative exposure and the dichotomous variable representing the valproate or lamotrigine/levetiracetam group will be tested for in each logistic and Cox PH model.
    b. The cumulative exposure variable will also be categorised empirically according to tertiles of the distribution to represent low, medium and high exposure to each of the three treatment groups separately, since the cumulative exposure pattern may be different for each treatment, plus thresholds cannot be defined a priori as cut-off points are not available by previous literature. For each exposure group (valproate, lamotrigine and levetiracetam) separately, a within-group analysis will be performed to study the dose-response relationship for each outcome by comparing high and medium exposure to treatment against low exposure to treatment as the referent category.
    c. For each outcome, a pre-defined list of covariates based on final models of primary comparative analyses will be forced into each of the aforementioned logistic and Cox PH model to provide estimates adjusted for relevant confounders. Since the distribution of cumulative exposure and of relevant confounders within each exposure group could differ from those of the other exposure groups, the results from the three within-exposure group analyses for each outcome will not be comparable.
11. *Narrow case definition for primary outcome - NDD*: This sensitivity analysis will use a narrow NDD composite case definition according to the following ICD-10 codes:

Clinical Code Description	**ICD-10**
Intellectual disability - mild	F70
Intellectual Disability - Moderate	F71

Clinical Code Description	ICD-10
Intellectual Disability -Severe	F72
Intellectual Disability -Profound	F73
Other Intellectual Disability	F78
Unspecified Intellectual Disability	F79
Specific developmental disorders of speech and language	F80
Specific developmental disorders of scholastic skills	F81
Mixed specific developmental disorders	F83
Childhood autism	F84.0
Atypical autism	F84.1
Other childhood disintegrative disorder	F84.3
Asperger syndrome	F84.5
Other pervasive developmental disorders	F84.8
Pervasive developmental disorder, unspecified	F84.9
Other disorders of psychological development	F88
Unspecified disorder of psychological development	F89
Dyslexia and other symbolic dysfunctions, not elsewhere classified	R48
Hyperkinetic disorders	F90
Specific developmental disorder of motor function	F82

This sensitivity analysis for the narrow NDD composite case definition only will be conducted in three parts:

a. Replication of the primary objective, with descriptive and comparative analyses as applied to the primary outcome cohort. Meta-analysis may be applied.
b. Replication of exploratory objective 5, with summary cohort characteristics and univariate analysis (section 9.7.3.1) performed to describe the subgroups and the risk factors for the narrow NDD composite outcome for offspring paternally exposed to valproate in combination with other AEDs (AED polytherapy) and offspring paternally unexposed to valproate but exposed to other AEDs (any combination) at the time of conception.
c. Replication of exploratory objective 6, with an exploratory sibling-matched descriptive analyses conducted on the narrow NDD composite outcome whereby only families with paternal valproate exposure-discordant siblings will be included (at least one offspring with paternal valproate exposure and one offspring without exposure).

9.7.6 Meta-analyses

Assuming country-specific analyses have been completed, results for the primary outcome analysis of NDD can also be combined across all three countries using a meta-analysis approach in order to achieve a more precise estimate of the observed effect size and identify any potential country-specific patterns in the data. A random effects meta-analysis will be applied assuming such heterogeneity in treatment effects exists. Cumulative incidence proportions and cumulative incidence rates of the two different exposure groups will be combined across the three databases. The HR of NDD including ASD in offspring paternally exposed to compared with offspring paternally exposed to lamotrigine or levetiracetam (composite monotherapy) will be calculated across the three databases

Results for the secondary outcome analysis of CM may also be similarly combined, although restricted to Norway and Denmark data only. The cumulative incidence proportion of the two

different exposure groups will be combined across the two databases, as well as the OR of CM in the two different exposure groups. The different start date for follow-up due to different data availability in the two countries can lead to heterogeneity in the type and nature of CM recorded, which in turn can have an impact on the precision of the estimate (see section 9.9 about limitations). For this reason a random effect meta-analysis will be conducted (53).

Between-database heterogeneity will be quantified with the I^2 measure; results will be pooled using inverse variance weighting, where estimates with a lower variance are assigned a higher weight in the pooled estimate.

In order to meta-analyse cumulative incidence proportions (for both NDD including ASD and CM composite outcomes), risk ratio estimates will be obtained in each country as the ratio of the risk in the valproate paternally exposed group to the risk in the lamotrigine/levetiracetam paternally exposed group; inverse variance weighting will then be applied to the risk ratios. For cumulative incidence rate (for NDD including ASD composite outcome), the inverse variance weighting method will be applied to rate ratios (obtained as the ratio of the incidence rate in the valproate paternally exposed group to the rate in the lamotrigine/levetiracetam group). Hazard ratios from Cox PH regression analysis will be pooled across the three databases after having applied a logarithmic transformation; OR from logistic regression analysis will also be pooled across the Norway and Denmark databases; inverse variance weighting will be applied to these models' estimates.

9.7.7 Handling of Missing Data

Missing data are those where a variable is directly reported as missing or unavailable, where a variable observation is blank, where the extracted data may not be interpretable, or where the value must be imputed to be missing because of data inconsistency or out-of-range results.

Methods to handle issues of missing or conflicting data, will be summarised within the detailed study specific SAP which will be constructed to assist data analysis. In summary, the degree of data completeness and patterns of missingness will be summarized for all covariates proposed for inclusion in the regression analysis of the primary outcome of interest, and the regression analysis of the secondary outcome of interest using a pattern of missingness matrix. The number and proportion of missing data for each variable and the top five most frequent patterns of missingness will be presented. This descriptive analysis will be performed in order to explore which covariates have non-trivial proportions of missing data (>5%) and to examine the plausibility of the missing at random (MAR) assumption to justify any subsequent regression methods. A sensitivity analysis may be conducted to explore the impact of non-trivial proportions of missing data among key covariates and the subsequent bias that may occur in analyses restricted to participants with complete data ("complete case analysis") as in the primary and secondary outcome analysis. Appropriate imputation methods will be dependent on the amount of missing data and data type but may include use of the Multiple Imputation by Chained Equations (MICE).

9.8 Quality Control

The study will use existing databases, which are being used widely for research. The study will be executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional PASS, including but not limited to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols (Annex 2. ENCePP checklist for study protocols), and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE

GPP) as well as the specific IQVIA Standard Operating Procedures (SOPs) on retrospective analysis.

For the IQVIA EU data sources, quality control is conducted at several levels depending on the database. At the database level, the quality unit of the production department of IQVIA verifies continuously the quality of its sources in terms of representativeness and consistency of collected data. All study programs, log files, and output files will be stored on the secure server. If the study is being conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures.

9.9 Limitations of the Research Methods

9.9.1 Database limitations

The individual study databases have limitations typical of other registries databases:

- Data are collected only for administrative purposes, so some medical information not directly related to reimbursement may be incomplete or not available at all.
- As the data will be extracted from different country registries, some differences are expected in terms of variables collected, coverage and missing data patterns.
- Due to the imperative need to have family linkage of data, this study proposes to use databases from Norway, Sweden and Denmark, which allow this possibility. These countries are close from each other and all from the North of Europe. However, an important consideration in choice of study population is the generalizability (external validity) of the data source within a country, which can be defined as the degree to which the population covered by the database is representative of the total population.
- National databases such as those from the Nordic countries are known to be representative of the population of the country, typically contain lifetime data of patients and have demonstrably been used for research to reveal the real-world patterns. Furthermore more, choice of country and database selection is based on the ability for longitudinal record linkage between father, mother and offspring; this being a key requirement for this study.
- With regard to understanding the impact of genetic variability, this study will inform on whether an association exists between paternal use of AED in the pre-conception period and adverse effects in the offspring. Information on genetic profiling and ethnicity is not being collected therefore an evaluation of the hypothesised genetic mechanism for the proposed adverse effects, although relevant to the ongoing investigation, is not possible in this study.
- Information on breastfeeding is not available for Sweden and Norway, only limited data after 2012 for Denmark.
- Linkage to the father is not possible for induced abortion records in any country at study. It means that all diagnosis of CM followed by an induced abortion are not

detectable[19] and not included in this study. It can lead to a selection of cases and to a survivor bias.

- Misclassification of paternal linkage is possible where the registered father is not the biological father of the offspring. All countries of interest include within their registries the possibility of identification of adoption or IVF. Offspring who were adopted or resulting from IVF are not included in this study. Paternal discrepancy can occur also when the offspring is identified as being biologically fathered by someone other than the man who believes he is the father. This was investigated by Bellis et al (54) who concluded that median paternal discrepancy is 3.7% (IQR=2.0%–9.6%).
- Information about spontaneous abortions and stillbirths (linked to mother and father) are not available for Denmark until 22nd week of pregnancy and for Norway until 12th week. It means that all diagnosis of CM for spontaneous abortions/stillbirths occurred before these weeks of gestation are not detectable and not included in this study. It can lead to a selection of cases and to a survivor bias. For purposes of the secondary analysis for CM, this will be conducted in Denmark and Norway only, where paternal linkage to non-live births is feasible. Sweden, where the linkage with fathers is not possible for non-live births, is not included in this analysis. However an exploratory analysis is proposed to explore risk of CM in live births, for completeness. The implications of having different definitions of the index date for the three countries should also be acknowledged. In brief, the relationship between the impact of a maternal exposure to a teratogen on normal embryonic and fetal differentiation and morphogenesis and week of gestation is well known. The distribution of type of CM and severity is likely to be different. Where data will be collected from 12th week of gestation, the distribution is likely to be biased towards major morphological abnormalities of which a high proportion will have a fatal outcome. Conversely where data are collected from 22nd week of gestation (Denmark) and from birth date of offspring (Sweden), the distribution is likely to favour functional defects and minor morphological abnormalities of which a high proportion will survive to term. In this regard the heterogeneity of outcome could be profound and have an impact on the precision of the estimate.
- Information on medicines without prescription purchased from a retailer is not available in the registers. It is a major limitation for medicines like folic acid that has a significative impact on frequency of Neural Tube Defects (NTD) and congenital heart defects (CHD). The findings of the Hungarian intervention (randomized double-blind and cohort controlled) trials indicated that periconceptional folic acid (FA)-containing multivitamin supplementation prevented the major proportion (about 90%) of NTD as well as a certain proportion (about 40%) of CHD defects (55). It is also reported in the literature that lack of folic acid supplementation in women with epilepsy treated with AED is associated with an 6-fold increased risk of autistic traits in their offspring at 18 months, or an eight fold increase in their offspring at 36 months

[19] In Denmark, induced abortion is allowed by law until 12 week of pregnancy, but a woman may also be granted an authorisation to abort after 12 weeks if certain circumstances are proved to be present (such as poor socioeconomic condition of the woman; risk of birth defects to foetus; the pregnancy being the result of rape; mental health risk to mother). In Norway, current legislation provides abortion on request in the first 12 weeks of gestation, by application up to the 18th week, and thereafter only under special circumstances until the foetus is viable.

depending on the instrument used, although this does not imply an increased risk of autism (56). The impact of failing to account for folic acid supplementation as an important confounder could lead to a bias in either direction in the estimate of risk of the pooled composite outcome of CM, or the pooled composite outcome of NDD, including ASD, in both exposure groups, however this is anticipated to be non-differential.

- Lifestyle factors (such as smoking or alcohol consumption) may not be available or may be incomplete. The negative effects of Prenatal Alcohol Exposure (PAE) on the developing brain and the resulting neurological and/or cognitive, behavioural, emotional, and adaptive functioning deficits in offspring maternally exposed *in utero* are well recognised (57). Alcohol-related NDD (ARND) refers to a complex range of disabilities in neurodevelopment and behaviour. Unlike Foetal Alcohol Syndrome (FAS), confirmed PAE cannot be identified phenotypically and therefore misclassification with other NDD or affective disorder is possible. Current prevalence estimates for FAS range from 0.5 to 7 cases per 1,000 live births in the United States, and the prevalence of FAS and ARND combined is thought to be three times that of FAS alone. In this study, there is no specific information on alcohol consumption and therefore the association between alcohol and ARND cannot be studied. Nevertheless, the potential impact on this study an overestimate of up to seven cases of the primary outcome of NDD per 1000 pregnancies when the alternative cause was potentially alcohol. However, this is anticipated to be non-differential, affecting both exposure groups equally.
- It is also well established that prenatal nicotine exposure, even through maternal smokeless tobacco use, is associated with numerous postnatal adverse health outcomes in newborns – not only low birth weight, preterm delivery, and sudden infant death syndrome but also severe neuropsychiatric disorders (58) (Tourette syndrome and chronic tic disorder (TS/CT), as well as TS/CT with comorbid psychiatric conditions including attention-deficit/hyperactivity disorder [ADHD]). With an estimated prevalence of up to ten cases per 1000 pregnancies the impact of misclassification can lead to an over estimation of effect of AED monotherapy on risk when the alternative cause was potentially prenatal nicotine. However, this is anticipated to be non-differential, affecting both exposure groups equally.
- In terms of the parental intelligence quotient (IQ) levels, such data are not available specifically in the registries and surrogate measures are often utilised. The potential impact of such missing data in this study is unclear, since there is conflicting evidence in the literature about the association between maternal AED exposure, maternal IQ and NDD in offspring. In a large prospective, observational, multicentre study, where data were available, the relationship between maternal IQ, maternal AED exposure and NDD (based on offspring IQ) in the offspring did not identify parental IQ as a risk factor (59). Conversely the results of a meta-analysis suggested higher parental IQ (based on a surrogate measure - parental education) is associated with increased risk of ASD (60) as a subtype of NDD (maternal education college graduate+[RR=1.58, 95% CI: 1.33, 1.88; P<.001], paternal education college graduate+[RR=1.54, 95% CI: 1.28, 1.87; P<.001]). Therefore, although potentially an important risk factor, the resulting bias from missing information may be in either direction and is also likely to be non-differential.

- Information on socioeconomic status (SES) is also not specifically available in the Nordic registries and surrogate measures are again often utilised. Similar to missing data for IQ, the potential impact on this study is unclear because conflicting evidence also exists in the literature. Epidemiological studies in the US consistently find ASD to be overrepresented in high SES families. However, a case-control study based within a Swedish county using council data reports that an inverse relationship exists such that risk is highest in subjects from lower SES (61). Their hypothesis for other studies not observing this relationship is based on under ascertainment of cases from lower SES groups in those studies. This is echoed in another recent publication in the US (62). It is also acknowledged that severe early deprivation has a causal role in NDD such as ADHD and is likely to apply to conditions such as ASD (63). The HOME scale for measuring adversity, does appear to correlate with risk of ADHD specifically, however more research is required to ascertain whether this is a causal association and the direction of causation (64). In summary, given these uncertainties, for this study, missing data on parental IQ and HOME are not considered a major limitation.
- Environmental and viral toxic substances factors are not available.
- For Scandinavian registry data, relatively long lag times has to be considered and they vary by country, for example the Swedish National Patient Register annual uptake is completed in September of the following year.
- For Denmark, when the outcome for a specific analysis will have less than five cases/observations, the specific result and other potentially related results, that could lead to the identification of those patients, will not be delivered from the data provider. It is a potential limitation for analyses that require many subclassifications, restrictions and stratifications, such as the exploratory analysis to investigate the risk of CM by target body system organ class. Furthermore, minimum and maximum values cannot be reported.

9.9.2 Study analysis limitations

- Restriction to monotherapy could lower the generalizability of the results due to differences in real life clinical practice. One study found that approximately half of the population become seizure free on their first drug (65), while others need to switch or add additional AEDs. The selection of the cohort for analysis for the primary objective based on paternal valproate or lamotrigine/levetiracetam monotherapy use could potentially result in a small population, and therefore could be underpowered if the sample size falls below that required to detect the desired HR of interest. In the present study, patients who are on AED polytherapy are excluded from the primary analysis. To understand the population of AED polytherapy users, descriptive analysis will be conducted as an exploratory objective. Moreover, during the 3 months prior to LMP2, a father can be exposed to more than one AED in a sequence of monotherapies, that is an exposure to multiple drugs in the period at study, a polytherapy. For this reason, switchers are considered being in AED polytherapy treatment, therefore excluded from the comparative analyses. However, the frequency of switchers will be described.
- It is expected that few offspring will be both paternally and maternally exposed to AEDs, however there will likely be some. Offspring who fall into this category will be excluded in the primary comparative analysis. However, the descriptive analyses of the overall cohort will inform on the understanding of the characteristics of these offspring.

- The exposure window that affects the outcomes of the study could be shorter than the complete 3 months spermatogenic cycle. If so, the methodology used to assess paternal exposure may be able to examine the effect of proximity to conception, in that only selected clusters of paternal exposure can be evaluated. However, this restriction could result in very small sample size. Therefore, the rates of NDD could be under-estimated and the HR estimates of NDD could be biased towards the null.
- It is known that the exposure of AEDs and other medications during breastfeeding is associated with the outcomes of interest. Failing to account for exposure during breastfeeding could lead residual confounding. Breastfeeding data is only available for Denmark and only after 2012.
- Hospitalizations and outpatient visits within secondary care are comprehensively covered in the National Patient Registers in Denmark, Norway and Sweden. However, diagnosis of NDD can be challenging, since there is a lack of specific medical tests to diagnoses disorders, especially ASD. Specialists must assess behaviour; anomalies not being evident for a number of years after birth. Indeed, subjects may not receive a final diagnosis until much older. The impact of this study is that there may be differences in the identification of certain disorders over other as well as under-recording. However, this is not expected to be differential between the paternal exposure groups. Nevertheless, when evaluating the quality of the childhood ASD diagnosis in the Danish Psychiatric Central Register, it was found that 94% of the childhood ASD diagnoses met the ICD-10 criteria for a correct diagnosis'(66). Therefore, the identification of ASD cases by ICD-10, as proposed in this study, is valid.
- In the case an offspring may have no contact with the health care system for an extended period time, that individual could potentially experience an outcome before it can be recorded. This could cause a delayed diagnosis observation and immortal time bias.
- All relevant measured covariates will be entered into the model for the primary analysis. However, given that registries may not contain information on all relevant known and unknown confounding variables, residual confounding may still be present in the study results. Descriptive analysis and handling of missing data will be conducted as reported in section 9.7.6.
- It is assumed in these analyses that all prescribed drugs are filled and then taken by patients in a compliant manner. Non-compliance would result in misclassification of exposure and could cause an underestimation of the association between exposure and outcome.
- Failure in family linkage may be a limitation in the proposed analysis, particularly if a high proportion of the eligible population to be included in the study cannot be linked within-family units. Examination of characteristics of excluded subjects from linkage is recommended.
- The descriptive analysis of exposure-discordant siblings will not allow result in conclusions about the underlying causality mechanism.
- There might be additional conditions/events occurring during childhood that are associated with NDD/cognitive impairment such as Trisomy, some infectious diseases such as measles or meningitis, brain trauma, etc. These potential risk factors/confounders were not included in this study, but most probably would not lead to a differential bias across exposure groups.

9.10 Other Aspects

9.10.1 Changes to the Protocol

All changes post-approval are detailed in Section 5.

9.10.2 Study Management

This study will be performed by IQVIA, with guidance, input, review and approval of Sanofi and the members of the Marketing Authorisation Holder Consortium, including development of materials, data management, analysis and reporting.

10. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the guidelines for good pharmacovigilance practices (GVPs) and GPP issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations.

10.1 Independent Ethics Committee/Institutional Review Board

The study protocol will be submitted to the responsible Institutional Review Board (IRB) / Independent Ethics Committee (IEC) for its review / approval whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to Ethics Review Boards (ERBs) and regulatory authorities as required by local laws and regulations.

When the approval has been granted, the formal procedure of applying for access to and retrieval of patient-level health information can be performed to each governing health authority in the respective Nordic country. A prerequisite for approval from an ERB is that the research project is thoroughly described in a study protocol with a clear scientific objective and purpose. In addition, the ethics application and approval for data extraction are now combined in Denmark and Norway. Accordingly, the overall ethical review time is estimated to take 6-12 months.

This study is non-interventional and analysis is based on secondary data use. No identifying data is collected or stored by IQVIA in any of the planned approaches.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will adhere to the International Society for Pharmacoepidemiology (ISPE) good pharmacoepidemiology practice guidelines. This is a non-interventional study design which is based on secondary data use. Expedited reporting of Adverse Events (AE) and Adverse Drug Reactions (ADR) is not required. This PASS is designed to provide data on paternal exposure to AEDs and adverse outcomes in offspring, based on aggregate analyses.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 Progress Reports *(If Applicable)*

Due to the long anticipated time for data ethics and extraction in Nordic countries, a progress report will be submitted 12 months after the PRAC endorsement.

12.2 Interim Analyses and Reporting

An interim report will be submitted 6 months after the progress report, upon the first country(ies) data available.

12.3 Final Analyses and Reporting

The interim/progress report(s) and the final study report will be written in accordance with the GVP guidelines module VIII (EMA/813938/2011).

In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC), information about this PASS will be entered into the publicly available EU PAS register (http://www.encepp.eu/encepp/studiesDatabase.jsp). The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

12.4 Publications

Study findings will be published in a peer reviewed journal.

Any publication will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE), updated April 2010.

All reporting will be consistent with the STROBE Initiative checklist for cohort studies (STROBE 2008).

Still in line with the EMA guideline, and in order to allow competent authorities to review in advance the results and interpretations to be published, the MAHs should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

13. REFERENCES

1. European Medicines Agency (EMA). PRAC recommends strengthening the restrictions on the use of valproate in women and girls [Internet]. 2014 [cited 2018 Oct 2]. Available from: https://www.ema.europa.eu/news/prac-recommends-strengthening-restrictions-use-valproate-women-girls

2. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA. 2013 Apr 24;309(16):1696.

3. Engeland A, Bjørge T, Daltveit AK, Skurtveit S, Vangen S, Vollset SE, et al. Effects of preconceptional paternal drug exposure on birth outcomes: cohort study of 340 000 pregnancies using Norwegian population-based databases: Effects of paternal drug exposure on birth outcomes. Br J Clin Pharmacol. 2012 Aug;75(4):1134–41.

4. Ibi D, Fujiki Y, Koide N, Nakasai G, Takaba R, Hiramatsu M. Paternal valproic acid exposure in mice triggers behavioral alterations in offspring. Neurotoxicol Teratol. 2019 Dec;76:106837.

5. Trasler JM, Doerksen T. Teratogen update: paternal exposures-reproductive risks. Teratology. 1999 Sep;60(3):161–72.

6. Yang F, Chen J, Miao MH, Yuan W, Li L, Liang H, et al. Risk of autism spectrum disorder in offspring following paternal use of selective serotonin reuptake inhibitors before conception: a population-based cohort study. BMJ Open. 2017 Dec;7(12):e016368.

7. Wallenius, M, Lie, E, Daltveit, AK, Salvesen, KÅ, Skomsvoll, JF, Kalstad, S, et al. No Excess Risks in Offspring With Paternal Preconception Exposure to Disease-Modifying Antirheumatic Drugs. ARTHRITIS & RHEUMATOLOGY. 2015 Jan;67(1):296–301.

8. Engeland A, Bramness JG, Daltveit AK, Rønning M, Skurtveit S, Furu K. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106 000 pregnancies in Norway 2004–2006. Br J Clin Pharmacol. 2008 May;65(5):653–60.

9. Veiby G, Daltveit AK, Schjølberg S, Stoltenberg C, Øyen AS, Vollset SE, et al. Exposure to antiepileptic drugs in utero and child development: A prospective population-based study. Epilepsia. 2013 Aug;54(8):1462–72.

10. Coste J, Blotiere PO, Miranda S, Mikaeloff Y, Peyre H, Ramus F, et al. Risk of early neurodevelopmental disorders associated with in utero exposure to valproate and other antiepileptic drugs: a nationwide cohort study in France. Sci Rep. 2020 Oct 22;10(1):17362.

11. Blotière PO, Miranda S, Weill A, Mikaeloff Y, Peyre H, Ramus F, et al. Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study. BMJ Open. 2020 Jun 7;10(6):e034829.

12. Christensen J, Grønborg TK, Sørensen MJ, Schendel D, Parner ET, Pedersen LH, et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. JAMA. 2013 Apr 24;309(16):1696–703.

13. Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring. JAMA Netw Open. 2019 Jan 4;2(1):e186606.

14. St. Louis E. Truly "Rational" Polytherapy: Maximizing Efficacy and Minimizing Drug Interactions, Drug Load, and Adverse Effects. Curr Neuropharmacol. 2009 Jun 1;7(2):96–105.

15. Hurault-Delarue C, Chouquet C, Savy N, Lacroix I, Beau AB, Montastruc JL, et al. How to take into account exposure to drugs over time in pharmacoepidemiology studies of pregnant women?: New Method to Study Drug Exposure During Pregnancy. Pharmacoepidemiol Drug Saf. 2016 Jul;25(7):770–7.

16. Wood ME, Lupattelli A, Palmsten K, Bandoli G, Hurault-Delarue C, Damase-Michel C, et al. Longitudinal Methods for Modeling Exposures in Pharmacoepidemiologic Studies in Pregnancy. Epidemiol Rev. 2021 Jun 8;

17. Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK, et al. Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations. N Engl J Med. 2010 Jun 10;362(23):2185–93.

18. EUROCAT (2013). EUROCAT Guide 1.4: Instruction for registration of congenital anomalies. [Internet]. 2013 [cited 2019 Mar 5]. (EUROCAT Central Registry, University of Ulster). Available from: https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/Full_Guide_1_4_version_28_DEC2018.pdf

19. Janecka M, Mill J, Basson MA, Goriely A, Spiers H, Reichenberg A, et al. Advanced paternal age effects in neurodevelopmental disorders—review of potential underlying mechanisms. Transl Psychiatry. 2017 Jan;7(1):e1019–e1019.

20. Hultman CM, Sandin S, Levine SZ, Lichtenstein P, Reichenberg A. Advancing paternal age and risk of autism: new evidence from a population-based study and a meta-analysis of epidemiological studies. Mol Psychiatry. 2011 Dec;16(12):1203–12.

21. Green RF, Olney S, Crider K, Olney R, Archer N, Olshan A, et al. Association of Paternal Age and Risk for Major Congenital Anomalies from the National Birth Defects Prevention Study, 1997–2004. Ann Epidemiol. 2010;20(3):241–9.

22. Cioppi F, Casamonti E, Krausz C. Age-Dependent De Novo Mutations During Spermatogenesis and Their Consequences. Adv Exp Med Biol. 2019;1166:29–46.

23. Peng J, Meng Z, Zhou S, Zhou Y, Wu Y, Wang Q, et al. The non-genetic paternal factors for congenital heart defects: A systematic review and meta-analysis. Clin Cardiol. 2019 May 29;clc.23194.

24. Excellence NTNI for H and C. BNF: British National Formulary - NICE [Internet]. [cited 2019 Jul 30]. Available from: https://bnf.nice.org.uk/drug/sodium-valproate.html

25. Tomson T, Xue H, Battino D. Major congenital malformations in children of women with epilepsy. Seizure. 2015 May 1;28:46–50.

26. Sundelin HEK, Larsson H, Lichtenstein P, Almqvist C, Hultman CM, Tomson T, et al. Autism and epilepsy: A population-based nationwide cohort study. Neurology. 2016 Jul 12;87(2):192–7.

27. Bitsika V, Sharpley CF, Andronicos NM, Agnew LL. Prevalence, structure and correlates of anxiety-depression in boys with an autism spectrum disorder. Res Dev Disabil. 2016 Mar;49–50:302–11.

28. Lever AG, Geurts HM. Psychiatric Co-occurring Symptoms and Disorders in Young, Middle-Aged, and Older Adults with Autism Spectrum Disorder. J Autism Dev Disord. 2016 Jun;46(6):1916–30.

29. May ME, Kennedy CH. Health and Problem Behavior Among People With Intellectual Disabilities. Behav Anal Pract. 2010 Dec;3(2):4–12.

30. Kellogg M, Meador KJ. Neurodevelopmental Effects of Antiepileptic Drugs. Neurochem Res. 2017 Jul;42(7):2065–70.

31. Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, et al. Ethosuximide, Valproic Acid, and Lamotrigine in Childhood Absence Epilepsy. N Engl J Med. 2010 Mar 4;362(9):790–9.

32. Zomerdijk I, Ruiter R, Houweling L, Herings R, Straus S, Stricker B. Dispensing of potentially teratogenic drugs before conception and during pregnancy: a population-based study. BJOG Int J Obstet Gynaecol. 2015 Jul;122(8):1119–29.

33. Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, et al. Trends in the prevalence of developmental disabilities in US children, 1997-2008. Pediatrics. 2011 Jun;127(6):1034–42.

34. Bech LF, Polcwiartek C, Kragholm K, Andersen MP, Rohde C, Torp-Pedersen C, et al. In utero exposure to antiepileptic drugs is associated with learning disabilities among offspring. J Neurol Neurosurg Psychiatry. 2018 Dec;89(12):1324–31.

35. Tsiropoulos I, Gichangi A, Andersen M, Bjerrum L, Gaist D, Hallas J. Trends in utilization of antiepileptic drugs in Denmark. Acta Neurol Scand. 2006 Jun;113(6):405–11.

36. PxWeb - välj tabell [Internet]. [cited 2019 Aug 21]. Available from: http://www.statistikdatabasen.scb.se/pxweb/sv/ssd/

37. Ehrenstein V, Kristensen NR, Monz BU, Clinch B, Kenwright A, Sørensen HT. Oseltamivir in pregnancy and birth outcomes. BMC Infect Dis. 2018 Oct 16;18(1):519.

38. Schmidt RJ, Schroeder DI, Crary-Dooley FK, Barkoski JM, Tancredi DJ, Walker CK, et al. Self-reported pregnancy exposures and placental DNA methylation in the MARBLES prospective autism sibling study. Environ Epigenetics. 2016 Dec;2(4):dvw024.

39. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable Selection for Propensity Score Models. Am J Epidemiol. 2006 Jun 15;163(12):1149–56.

40. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med. 1989 May;8(5):551–61.

41. Frank E, Harrell J. Regression Modeling Strategies. With Applications to Linear Models, Logistic Regression, and Survival Analysis. New York: Springer; 2011.

42. Chen T, Guestrin C. XGBoost: A Scalable Tree Boosting System. In: Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining - KDD '16 [Internet]. San Francisco, California, USA: ACM Press; 2016 [cited 2019 Mar 26]. p. 785–94. Available from: http://dl.acm.org/citation.cfm?doid=2939672.2939785

43. Lunceford JK, Davidian M. Stratification and weighting via the propensity-score in estimation of causal treatment effects: a comparative study. Stat Med. 2004 Oct 15;23(19):2937–60.

44. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med. 2009 Nov 10;28(25):3083–107.

45. Austin PC, Mamdani MM. A comparison of propensity score methods: a case-study estimating the effectiveness of post-AMI statin use. Stat Med. 2006 Jun 30;25(12):2084–106.

46. Austin PC, Grootendorst P, Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Stat Med. 2007 Feb 20;26(4):734–53.

47. Agrawal S, Rao SC, Bulsara MK, Patole SK. Prevalence of Autism Spectrum Disorder in Preterm Infants: A Meta-analysis. Pediatrics. 2018 Sep;142(3).

48. Peralta-Carcelen M, Schwartz J, Carcelen AC. Behavioral and Socioemotional Development in Preterm Children. Clin Perinatol. 2018 Sep;45(3):529–46.

49. Broring T, Oostrom KJ, van Dijk-Lokkart EM, Lafeber HN, Brugman A, Oosterlaan J. Attention deficit hyperactivity disorder and autism spectrum disorder symptoms in school-age children born very preterm. Res Dev Disabil. 2018 Mar;74:103–12.

50. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiol Camb Mass. 1999 Jan;10(1):37–48.

51. Martens EP, Pestman WR, de Boer A, Belitser SV, Klungel OH. Systematic differences in treatment effect estimates between propensity score methods and logistic regression. Int J Epidemiol. 2008 Oct;37(5):1142–7.

52. Ali MS, Groenwold RHH, Klungel OH. Propensity Score Methods and Unobserved Covariate Imbalance: Comments on “Squeezing the Balloon”. Health Serv Res. 2014 Jun;49(3):1074–82.

53. Pastor DA, Lazowski RA. On the Multilevel Nature of Meta-Analysis: A Tutorial, Comparison of Software Programs, and Discussion of Analytic Choices. Multivar Behav Res. 2018 Feb;53(1):74–89.

54. Bellis MA, Huges K, Huges S, Ashton JR. Measuring paternal discrepancy and its public health consequences. J Epidemiol Community Health. 2005 Sep 1;59(9):749–54.

55. Czeizel AE, Dudás I, Vereczkey A, Bánhidy F. Folate Deficiency and Folic Acid Supplementation: The Prevention of Neural-Tube Defects and Congenital Heart Defects. Nutrients. 2013 Nov 21;5(11):4760–75.

56. Bjørk M, Riedel B, Spigset O, Veiby G, Kolstad E, Daltveit AK, et al. Association of Folic Acid Supplementation During Pregnancy With the Risk of Autistic Traits in Children Exposed to Antiepileptic Drugs In Utero. JAMA Neurol. 2017;75(2):160–8.

57. National Institute on Alcohol Abuse and Alcoholism (NIAAA). Recognizing Alcohol-Related Neurodevelopmental Disorder (ARND) in Primary Health Care of Children. In Interagency Coordinating Committee on Fetal Alcohol Spectrum Disorders (ICCFASD); 2011 [cited 2019 Mar 5]. Available from: https://www.niaaa.nih.gov/sites/default/files/ARNDConferenceConsensusStatementBooklet_Complete.pdf

58. Browne HA, Modabbernia A, Buxbaum JD, Hansen SN, Schendel DE, Parner ET, et al. Prenatal Maternal Smoking and Increased Risk for Tourette Syndrome and Chronic Tic Disorders. J Am Acad Child Adolesc Psychiatry. 2016;55(9):784–91.

59. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar;12(3):244–52.

60. Wang C, Geng H, Liu W, Zhang G. Prenatal, perinatal, and postnatal factors associated with autism: A meta-analysis. Medicine (Baltimore). 2017 May;96(18):e6696.

61. Rai D, Lewis G, Lundberg M, Araya R, Svensson A, Dalman C, et al. Parental socioeconomic status and risk of offspring autism spectrum disorders in a Swedish population-based study. J Am Acad Child Adolesc Psychiatry. 2012 May;51(5):467-476.e6.

62. Durkin MS, Maenner MJ, Baio J, Christensen D, Daniels J, Fitzgerald R, et al. Autism Spectrum Disorder Among US Children (2002–2010): Socioeconomic, Racial, and Ethnic Disparities. Am J Public Health. 2017 Nov;107(11):1818–26.

63. Wood AC, Rijsdijk F, Johnson KA, Andreou P, Albrecht B, Arias-Vasquez A, et al. The relationship between ADHD and key cognitive phenotypes is not mediated by shared familial effects with IQ. Psychol Med. 2011 Apr;41(4):861–71.

64. Lai WW, O'Mahony M, Mulligan A. The Home Observation Measure of the Environment is associated with symptoms of ADHD and oppositionality in a CAMHS sample. Clin Child Psychol Psychiatry. 2018 Oct 1;23(4):503–13.

65. Mayo Clinic. Epilepsy [Internet]. 2019. Available from: https://www.mayoclinic.org/diseases-conditions/epilepsy/diagnosis-treatment/drc-20350098

66. Lauritsen MB, Jorgensen M, Madsen KM, Lemcke S, Toft S, Grove J, et al. Validity of childhood autism in the Danish Psychiatric Central Register: findings from a cohort sample born 1990-1999. J Autism Dev Disord. 2010 Feb;40(2):139–48.

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title: A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorders as well as congenital abnormalities in offspring – a population-based retrospective study

EU PAS Register® number: EUPAS34201

Study reference number (if applicable): EMEA/H/A-31/1454

VALNAC09345

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[20]	☒	☐	☐	6
1.1.2 End of data collection[21]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.1, 7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	7.2, 9.5
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[20] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[21] Date from which the analytical dataset is completely available.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.2.2 9.7.3
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.3.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.1, 9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.2
	4.2.3 Country of origin	☒	☐	☐	9.1, 9.2.1
	4.2.4 Disease/indication	☒	☐	☐	9.3.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1, 9.2.3.1, 9.2.3.2
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3	Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2.1, 9.3.2.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2.1, 9.3.2.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2.2
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.3
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.2.2
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.2.3

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.3.1

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				

	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.1
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4.1

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section Number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4	Are stratified analyses included?	☒	☐	☐	9.7.2.1, 9.7.2.2
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3.1, 9.7.3.2.3, 9.7.5
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.3.2.3
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.7
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.5

Comments:

Section 11: Data management and quality control		**Yes**	**No**	**N/A**	**Section Number**
11.1	Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.2

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12.4

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.1, 9.9.2
12.1.2 Information bias?	☒	☐	☐	9.9.1, 9.9.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9.2
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	9.10.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.4

Comments:

Name of the main author of the protocol: Florent Richy

Date: 02/10/2023

Signature: DocuSigned by: Florent Richy 02DD3E57CC9C4B4...

ANNEX 3. ADDITIONAL INFORMATION

ANNEX 3A. INDICATION CODELISTS					
NORWAY, SWEDEN AND DENMARK REGISTRY					
Indications	**Definition**	**Nordic registry**	**Source of definition**	**Reference**	**Codelist tables in Annex 3F**
Epilepsy	Inpatient or outpatient event diagnosis based on ICD-10 codes	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	Jette N, Beghi E, Hesdorffer D, Moshé SL, Zuberi SM, Medina MT, et al. ICD coding for epilepsy: Past, present, and future-A report by the International League Against Epilepsy Task Force on ICD codes in epilepsy. Epilepsia. 2015 Mar;56(3):348–55.	Table 19
Bipolar affective disorder and Mania	Inpatient or outpatient event diagnosis based on ICD-10 codes Binary: yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Previous DUS study/literature/ NICE	1) Previous DUS study (in house) 2) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233. 3) Excellence N-TNI for H and C. BNF: British National Formulary - NICE [Internet]. [cited 2019 Apr 3]. Available from: https://bnf.nice.org.uk/drug/sodium-valproate.html#indicationsAndDoses 4) Vasudev K, Mead A, Macritchie K, Young AH. Valproate in acute mania: is our practice evidence based? Int J Health Care Qual Assur. 2012;25(1):41–52.	Table 18 Table 20

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; DUS: Drug utilization study; NICE: National Institute for Health and Care Excellence; S: Sweden; N: Norway; D: Denmark.

ANNEX 3B. PRIMARY ENDPOINT CODELISTS					
Endpoints	**Definition**	**Nordic Registry**	**Source of definition**	**Reference**	**Codelist tables in Annex 3F**
Autism spectrum disorder	First inpatient or outpatient event diagnosis (ICD-10 code) Binary: yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1)Yang F, Chen J, Miao M-H, Yuan W, Li L, Liang H, et al. Risk of autism spectrum disorder in offspring following paternal use of selective serotonin reuptake inhibitors before conception: a population-based cohort study. BMJ Open. 2017 Dec;7(12):e016368. 2) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233.	Table 8
Neurodevelopmental disorders	First inpatient or outpatient event (ICD-10 code) recorded for the child within outcome follow-up period Binary: yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Harris JC. New classification for neurodevelopmental disorders in DSM-5. Curr Opin Psychiatry. 2014 Mar;27(2):95–7. 2)Yang F, Chen J, Miao M-H, Yuan W, Li L, Liang H, et al. Risk of autism spectrum disorder in offspring following paternal use of selective serotonin reuptake inhibitors before conception: a population-based cohort study. BMJ Open. 2017 Dec;7(12):e016368. 3) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233.	Table 9 Table 10

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisiony; S: Sweden; N: Norway; D: Denmark.

ANNEX 3C. SECONDARY ENDPOINT CODELISTS					
Endpoints	**Definition**	**Nordic registry**	**Source of definition**	**Reference**	**Codelist tables in Annex 3F**
Congenital malformation (Major)	Congenital malformations are evaluated in inpatient or outpatient event diagnosis (ICD-10 code) among live births within 12 years after birth and among spontaneous abortion/stillbirths certificates (Norway and Denmark only) in second and third trimester of pregnancy	S: National Patient Registry and Medical Birth Registry; N: National Patient/Hospital Registry and Medical Birth Registry; D: National Patient Registry and Medical Birth Registry	Literature/EUROCAT	1) EUROCAT (2013). EUROCAT Guide 1.4: Instruction for registration of congenital anomalies. [Internet]. 2013 [cited 2019 Mar 5]. (EUROCAT Central Registry, University of Ulster). Available from: http://www.eurocat-network.eu/content/Full%20Guide%201%204%20version%2028_DEC2018.pdf 2) Ehrenstein V, Kristensen NR, Monz BU, Clinch B, Kenwright A, Sørensen HT. Oseltamivir in pregnancy and birth outcomes. BMC Infect Dis. 2018 Oct 16;18(1):519.	Table 11 Table 12
Congenital malformation (Minor)				3) Francine R, Pascale S, Aline H. Congenital Anomalies: Prevalence and Risk Factors. Univers J Public Health. 2014;7. 4) Jentink J, Loane MA, Dolk H, Barisic I. Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations. N Engl J Med. 2010;9. 5) Fetal Valproate Syndrome [Internet]. NORD (National Organization for Rare Disorders). [cited 2019 Mar 28]. Available from: https://rarediseases.org/rare-diseases/fetal-valproate-syndrome/	Table 13

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; S: Sweden; N: Norway; D: Denmark, EUROCAT: European Survaillance Congenital Anomalies.

ANNEX 3D. POTENTIAL RISK FACTORS CODELISTS for NDD					
Mothers					
Endpoints	**Definition**	**Nordic registry**	**Source of definition**	**Reference**	**Codelist tables in Annex 3F**
Maternal Age	maternal age at child birth; continuous	S: Multigenerational Register; N: Central Person Register; D: The Danish Civil Registration System	Literature	1) Sandin S, Hultman CM, Kolevzon A, Gross R, MacCabe JH, Reichenberg A. Advancing Maternal Age Is Associated With Increasing Risk for Autism: A Review and Meta-Analysis. Journal of the American Academy of Child & Adolescent Psychiatry. 2012 May;51(5):477-486.e1.	NA
Maternal Obesity	ICD-10 codes for the mother at least once in the 12 months look back from LMP2; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Edlow AG. Maternal obesity and neurodevelopmental and psychiatric disorders in offspring. Prenat Diagn. 2017 Jan;37(1):95–110. 2) Kong L, Norstedt G, Schalling M, Gissler M, Lavebratt C. The Risk of Offspring Psychiatric Disorders in the Setting of Maternal Obesity and Diabetes. Pediatrics. 2018 Sep 1;142(3):e20180776. Kong L, Norstedt G, Schalling M, Gissler M, Lavebratt C. The Risk of Offspring Psychiatric Disorders in the Setting of Maternal Obesity and Diabetes. Pediatrics. 2018 Sep 1;142(3):e20180776.	Table 45
Maternal Schizophrenia, schizotypal and delusional disorders (ever)	ICD-10 diagnosis for the mother in all the available data prior to index date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233. 2) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11.	Table 47
Maternal Affective Disorder (ever)	ICD-10 diagnosis for the mother in all the available data	S: National Patient Registry; N: National Patient/Hospital	Literature	1) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11.	Table 27 Table 28

ANNEX 3D. POTENTIAL RISK FACTORS CODELISTS for NDD					
	prior to index date; binary yes/no	Registry; D: National Patient Registry		2) Yang F, Chen J, Miao M-H, Yuan W, Li L, Liang H, et al. Risk of autism spectrum disorder in offspring following paternal use of selective serotonin reuptake inhibitors before conception: a population-based cohort study. BMJ Open. 2017 Dec;7(12):e016368.	
Maternal Neurotic Disorder (ever)	ICD-10 diagnosis for the mother in all the available data prior to index date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11.	Table 44
Maternal Rubella (DP)	ICD-10 diagnosis for the mother during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	Ornoy A, Weinstein- Fudim L, Ergaz Z. Genetic Syndromes, Maternal Diseases and Antenatal Factors Associated with Autism Spectrum Disorders (ASD). Front Neurosci [Internet]. 2016 Jul 6 [cited 2019 Mar 28];10. Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2016.00316/abstract	Table 46
Maternal CMV (DP)	ICD-10 diagnosis for the mother during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	Ornoy A, Weinstein- Fudim L, Ergaz Z. Genetic Syndromes, Maternal Diseases and Antenatal Factors Associated with Autism Spectrum Disorders (ASD). Front Neurosci [Internet]. 2016 Jul 6 [cited 2019 Mar 28];10. Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2016.00316/abstract	Table 31: CMV
Any concomitant medications associated with valproate-indicated psychiatric conditions (12 months look back from LMP2 and DP)	ATC codes for the mother at least once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	S and N: National Prescription Registry; D: Register of Medicinal Product Statistics	Literature	1) Bygdell M, Brunlöf G, Wallerstedt SM and Kindblom JM. Psychiatric adverse drug reactions reported during a 10-year period in the Swedish pediatric population. Pharmacoepidemiology and Drug Safety 2012; 21: 79–86 2) Dubovsky AN, Arvikar S, Stern TA, Axelrod L.The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited.Psychosomatics. 2012 Mar-Apr;53(2):103-15. doi: 10.1016/j.psym.2011.12.007.	Table 55

ANNEX 3D. POTENTIAL RISK FACTORS CODELISTS for NDD					
Any concomitant medications associated with neuropsychiatric adverse effects (12 months look back from LMP2 and DP)	ATC codes for the mother at least once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	S and N: National Prescription Registry; D: Register of Medicinal Product Statistics		3) Harro J.Neuropsychiatric Adverse Effects of Amphetamine and Methamphetamine.Int Rev Neurobiol. 2015;120:179-204. doi: 10.1016/bs.irn.2015.02.004. Epub 2015 Mar 12. 4) Thomas KH, Martin RM, Knipe DW, Higgins JP, Gunnell D. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ. 2015;350:h1109. Published 2015 Mar 12. doi:10.1136/bmj.h1109 5) Tuccori, M., Montagnani, S., Mantarro, S. et al.Neuropsychiatric Adverse Events Associated with Statins: Epidemiology, Pathophysiology, Prevention and Management CNS Drugs (2014) 28: 249. https://doi.org/10.1007/s40263-013-0135-1 6) Turjanski N and Lloyd GG. Psychiatric side-effects of medications: recent developments. Advances in psychiatric Treatment. 2005,11:58-70 7) Psychiatric side-effects of medications prescribed in internal medicine [Internet]. [cited 2019 Jul 31]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181628/	Table 54
Maternal Smoking (12 months look back from LMP2 and DP)	at least once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	Medical Birth Registry	Literature	Huang L, Wang Y, Zhang L, Zheng Z, Zhu T, Qu Y, et al. Maternal Smoking and Attention-Deficit/Hyperactivity Disorder in Offspring: A Meta-analysis. Pediatrics. 2018 Jan;141(1):e20172465.	NA
Maternal Substance abuse (12 months look back from LMP2 and DP)	ICD-10 diagnosis for the mother at least once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Frisher M, Collins J, Millson D, Crome, I. Problems of comorbid psychiatric illness and substance misuse in primary care in England and Wales. J Epi & Comm Health. 2005; 58(12): 1036-41 2) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233.	Table 48 Table 49
Maternal Alcohol abuse (12 months	ICD-10 diagnosis for the mother at least	S: National Patient Registry; N: National	Literature	1) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11.	Table 29 Table 30

ANNEX 3D. POTENTIAL RISK FACTORS CODELISTS for NDD					
look back from LMP2 and DP)	once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	Patient/Hospital Registry; D: National Patient Registry		2) Nielsen SM, Toftdahl NG, Nordentoft M, Hjorthøj C. Association between alcohol, cannabis, and other illicit substance abuse and risk of developing schizophrenia: a nationwide population-based register study. Psychol Med. 2017 Jul;47(9):1668-1677	
Maternal Diabetes (ever) and OR Gestational Diabetes (DP)	ICD-10 diagnosis for the mother in all the available data prior to index date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Ornoy A, Weinstein-Fudim L, Ergaz Z. Prenatal factors associated with autism spectrum disorder (ASD). Reprod Toxicol. 2015 Aug 15;56:155–69. 2) Xiang AH, Wang X, Martinez MP, Walthall JC, Curry ES, Page K, et al. Association of maternal diabetes with autism in offspring. JAMA. 2015 Apr 14;313(14):1425–34.	Table 37 Table 41
Fathers					
Endpoints	**Definition**	**Nordic registry**	**Source of definition**	**Reference**	**Codelist tables in Annex 3F**
Any concomitant medications associated with valproate-indicated psychiatric conditions (12 months look back from LMP2 and DP)	ATC codes for the father at least once in the 12 months look back from LMP2; binary yes/no	S and N: National Prescription Registry; D: Register of Medicinal Product Statistics	Literature	1) Bygdell M, Brunlöf G, Wallerstedt SM and Kindblom JM. Psychiatric adverse drug reactions reported during a 10-year period in the Swedish pediatric population. Pharmacoepidemiology and Drug Safety 2012; 21: 79–86 2) Dubovsky AN, Arvikar S, Stern TA, Axelrod L.The neuropsychiatric complications of glucocorticoid use: steroid psychosis revisited.Psychosomatics. 2012 Mar-Apr;53(2):103-15. doi: 10.1016/j.psym.2011.12.007. 3) Harro J.Neuropsychiatric Adverse Effects of Amphetamine and Methamphetamine.Int Rev Neurobiol. 2015;120:179-204. doi: 10.1016/bs.irn.2015.02.004. Epub 2015 Mar 12. 4) Thomas KH, Martin RM, Knipe DW, Higgins JP, Gunnell D. Risk of neuropsychiatric adverse events associated with varenicline: systematic review and meta-analysis. BMJ. 2015;350:h1109. Published 2015 Mar 12. doi:10.1136/bmj.h1109 5) Tuccori, M., Montagnani, S., Mantarro, S. et al.Neuropsychiatric Adverse Events Associated with Statins: Epidemiology, Pathophysiology, Prevention and Management CNS Drugs (2014) 28: 249. https://doi.org/10.1007/s40263-013-0135-1 6) Turjanski N and Lloyd GG. Psychiatric side-effects of medications: recent developments. Advances in psychiatric Treatment. 2005,11:58-70	Table 55
Any concomitant medications associated with valproate-indicated neuropsychiatric adverse effects (12 months look back from LMP2 and DP)	ATC codes for the father at least once in the 12 months look back from LMP2; binary yes/no	S and N: National Prescription Registry; D: Register of Medicinal Product Statistics	Literature		Table 54

ANNEX 3D. POTENTIAL RISK FACTORS CODELISTS for NDD					
				7) Psychiatric side-effects of medications prescribed in internal medicine [Internet]. [cited 2019 Jul 31]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181628/	
Paternal Schizophrenia, schizotypal and delusional disorders (ever)	ICD-10 diagnosis for the father in all the available data prior to conception; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233. 2) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11.	Table 47
Paternal Affective Disorder (excluding Bipolar and Mania) (ever)	ICD-10 diagnosis for the father in all the available data prior to conception; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11. 2) Yang F, Chen J, Miao M-H, Yuan W, Li L, Liang H, et al. Risk of autism spectrum disorder in offspring following paternal use of selective serotonin reuptake inhibitors before conception: a population-based cohort study. BMJ Open. 2017 Dec;7(12):e016368.	Table 28
Paternal Neurotic Disorder (ever)	ICD-10 diagnosis for the father in all the available data prior to conception; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11.	Table 44
Paternal Substance Abuse (12 months look back)	ICD-10 diagnosis for the father at least once in the 12 months look back from LMP2; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Frisher M, Collins J, Millson D, Crome, I. Problems of comorbid psychiatric illness and substance misuse in primary care in England and Wales. J Epi & Comm Health. 2005; 58(12): 1036-41 2) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233.	Table 49
Offspring					

ANNEX 3D. POTENTIAL RISK FACTORS CODELISTS for NDD					
Endpoints	**Definition**	**Nordic registry**	**Source of definition**	**Reference**	**Codelist tables in Annex 3F**
Offspring Gender	child gender at birth; binary male/female	Medical Birth Registry	Literature	Gershon J. A meta-analytic review of gender differences in ADHD. J Atten Disord. 2002 Jan;5(3):143–54.	NA
Offspring Fragile X Syndrome	ICD-10 diagnosis for the child between birth and exit date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Ehrenstein V, Kristensen NR, Monz BU, Clinch B, Kenwright A, Sørensen HT. Oseltamivir in pregnancy and birth outcomes. BMC Infect Dis [Internet]. 2018 Dec [cited 2019 Mar 28];18(1). Available from: https://bmcinfectdis.biomedcentral.com/articles/10.1186/s12879-018-3423-z 2) Jentink J, Loane MA, Dolk H, Barisic I. Valproic Acid Monotherapy in Pregnancy and Major Congenital Malformations. N Engl J Med. 2010;9. 3) Fetal Valproate Syndrome [Internet]. NORD (National Organization for Rare Disorders). [cited 2019 Mar 28]. Available from: https://rarediseases.org/rare-diseases/fetal-valproate-syndrome	Table 40
Offspring Lejeune/ cri du chat syndrome	ICD-10 diagnosis for the child between birth and exit date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature		Table 43
Offspring Tuberous sclerosis	ICD-10 diagnosis for the child between birth and exit date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature		Table 51

ANNEX 3D. POTENTIAL RISK FACTORS CODELISTS for NDD					
Offspring Congenital CMV	ICD-10 diagnosis for the child between birth and exit date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Ornoy A, Weinstein- Fudim L, Ergaz Z. Genetic Syndromes, Maternal Diseases and Antenatal Factors Associated with Autism Spectrum Disorders (ASD). Front Neurosci [Internet]. 2016 Jul 6 [cited 2019 Mar 28];10. Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2016.00316/abstract	Table 32
Offspring Congenital Rubella	ICD-10 diagnosis for the child between birth and exit date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Ornoy A, Weinstein- Fudim L, Ergaz Z. Genetic Syndromes, Maternal Diseases and Antenatal Factors Associated with Autism Spectrum Disorders (ASD). Front Neurosci [Internet]. 2016 Jul 6 [cited 2019 Mar 28];10. Available from: http://journal.frontiersin.org/Article/10.3389/fnins.2016.00316/abstract	Table 34
Offspring Foetal Alcohol syndrome	ICD-10 diagnosis for the child between birth and exit date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Underbjerg M, Kesmodel US, Landrø NI, Bakketeig L, Grove J, Wimberley T, Kilburn TR, Sværke C, Thorsen P, Mortensen EL. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on selective and sustained attention in 5-year-old children. BJOG 2012; DOI: 10.1111/j.1471-0528.2012.03396.x 2) Hagan JF, Balachova T, Bertrand J, Chasnoff I, Dang E, Fernandez-Baca D, et al. Neurobehavioral Disorder Associated With Prenatal Alcohol Exposure. PEDIATRICS. 2016 Oct 1;138(4):e20151553–e20151553.	Table 38
Offspring Epilepsy	ICD-10 diagnosis for the child between birth and exit date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Previous DUS study	Previous DUS study (in house)	Table 19

ATC: Anatomical Therapeutic Chemical; CMV: Cytomegalovirus; DP: during pregnancy; DUS: Drug utilization study; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; LMP2: Last Menstrual Period + 2 weeks; S: Sweden; N: Norway; D: Denmark; NA: Not Applicable.

ANNEX 3E. POTENTIAL CONFOUNDERS for NDD					
Fathers					
Endpoints	**Definition**	**Nordic registry**	**Source of definition**	**Reference**	**Codelist tables in Annex 3F**
Paternal Age	paternal age at child birth; continuous	S: Multigenerational Register; N: Central Person Register; D: The Danish Civil Registration System	Literature	1) D'Onofrio B.M., Rickert M.E., Frans E. Paternal age at childbearing and offspring psychiatric and academic morbidity. JAMA Psychiatry. 2014;71:432–438. 2) Miller B., Alaräisänen A., Miettunen J. Advanced paternal age, mortality and suicide in the general population. J Nerv Ment Dis. 2010;198:404–411. 3) Janecka M, Mill J, Basson MA, Goriely A, Spiers H, Reichenberg A, et al. Advanced paternal age effects in neurodevelopmental disorders—review of potential underlying mechanisms. Translational Psychiatry. 2017 Jan;7(1):e1019–e1019.	NA
Bipolar Affective Disorder and mania (ever)	ICD-10 diagnosis for the father in all the available data prior to conception; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Viktorin A, Levine SZ, Altemus M, Reichenberg A, Sandin S. Paternal use of antidepressants and offspring outcomes in Sweden: nationwide prospective cohort study. BMJ. 2018 Jun 8;k2233. 2) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11.	Table 18 Table 20

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; S: Sweden; N: Norway; D: Denmark; NA: Not Applicable.

ANNEX 3F. POTENTIAL RISK FACTORS CODELISTS for CM					
Mother					
Maternal Age	maternal age at index date (12th and 22th week of pregnancy respectively in Norway and Denmark); continuous	S: Multigenerational Register; N: Central Person Register; D: The Danish Civil Registration System	WHO	World Health Organization (WHO). Congenital anomalies [Internet]. WHO Official Website. 2016 [cited 2019 Mar 26]. Available from: https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies	NA
Maternal Obesity	ICD-10 for the mother at least once in the 12 months look back from LMP2; binary yes/no	S: Medical Birth Registry; N: Medical Birth Registry; D: Medical Birth Registry	Literature	1)Persson M, Cnattingius S, Villamor E, Söderling J, Pasternak B, Stephansson O, et al. Risk of major congenital malformations in relation to maternal overweight and obesity severity: cohort study of 1.2 million singletons. BMJ. 2017 Jun 14;357:j2563. 2)Madhab G, Bharadwaz A. Maternal Obesity and Congenital Anomalies: Its Implications and Future Trends. Journal of SAFOG. 2015 Dec;7(3):134–42.	Table 45
Maternal Diabetes (ever)	ICD-10 diagnosis for the mother in all the available data prior to index date; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK. Effect of maternal diabetes on the embryo, fetus, and children: Congenital anomalies, genetic and epigenetic changes and developmental outcomes: Maternal Diabetes and Pregnancy Outcome. Birth Defects Res Part C Embryo Today Rev. 2015 Mar;105(1):53–72.	Table 37
Maternal gestational diabetes (DP)	ICD-10 diagnosis for the mother in all the available data prior to index	S: Medical Birth Registry; N: Medical Birth Registry; D: Medical Birth Registry	Literature	1) Ornoy A, Reece EA, Pavlinkova G, Kappen C, Miller RK. Effect of maternal diabetes on the embryo, fetus, and children: Congenital anomalies, genetic and epigenetic changes and developmental outcomes: Maternal Diabetes and Pregnancy Outcome. Birth Defects Res Part C Embryo Today Rev. 2015 Mar;105(1):53–72.	Table 37

ANNEX 3F. POTENTIAL RISK FACTORS CODELISTS for CM					
	date; binary yes/no				
Maternal Rubella (DP)	ICD-10 diagnosis for the mother during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 Spring;40(2):99–114.	Table 46
Maternal Varicella (DP)	ICD-10 diagnosis for the mother during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 Spring;40(2):99–114.	Table 52
Maternal Toxoplasmosis (DP)	ICD-10 diagnosis for the mother during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 Spring;40(2):99–114.	Table 50
Maternal Herpes Simplex virus (DP)	ICD-10 diagnosis for the mother during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1)Ambroggio L, Lorch SA, Mohamad Z, Mossey J, Shah SS. CONGENITAL ANOMALIES AND RESOURCE UTILIZATION IN NEONATES INFECTED WITH HERPES SIMPLEX VIRUS. Sex Transm Dis. 2009 Nov;36(11):680–5. 2)Ferry T, Vial Y, Vaudaux B. [Varicella during pregnancy: consequences for the mother and the newborn]. Rev Med Suisse. 2011 Apr 27;7(292):900–4.	
Maternal CMV (DP)	ICD-10 diagnosis for the mother during	S: National Patient Registry; N: National Patient/Hospital	Literature	Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 Spring;40(2):99–114.	Table 31

ANNEX 3F. POTENTIAL RISK FACTORS CODELISTS for CM					
	pregnancy; binary yes/no	Registry; D: National Patient Registry			
Maternal Alcohol abuse (12 months look back from LMP2 and DP)	ICD-10 diagnosis for the mother at least once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1)Mesquita M dos A, Segre CA de M, Mesquita M dos A, Segre CA de M. Congenital malformations in newborns of alcoholic mothers. Einstein (São Paulo). 2010 Dec;8(4):461–6. 2)Grewal J, Carmichael SL, Ma C, Lammer EJ, Shaw GM. Maternal Periconceptional Smoking and Alcohol Consumption and Risk for Select Congenital Anomalies. Birth Defects Res A Clin Mol Teratol. 2008 Jul;82(7):519–26.	Table 29 Table 30
Maternal Substance abuse (12 months look back from LMP2 and DP)	ICD-10 diagnosis for the mother at least once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	S: National Patient Registry; N: National Patient/Hospital Registry; D: National Patient Registry	Literature	1) Jokiranta E, Brown AS, Heinimaa M, Cheslack-Postava K, Partanen A, Sourander A. Parental psychiatric disorders and autism spectrum disorders. Psychiatry Res. 2013 May 30;207(3):203–11. 2) Nielsen SM, Toftdahl NG, Nordentoft M, Hjorthøj C. Association between alcohol, cannabis, and other illicit substance abuse and risk of developing schizophrenia: a nationwide population-based register study. Psychol Med. 2017 Jul;47(9):1668-1677	Table 48 Table 49
Maternal Smoking (12 months look back from LMP2 and DP)	ICD-10 diagnosis for the mother at least once in the 12 months look back from LMP2 or during pregnancy; binary yes/no	Medical Birth Registry	Literature	1) Kallen K. Maternal smoking during pregnancy and infant head circumference at birth. Early Hum Dev. 2000 Jun;58(3):197–204. 2) Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. Human Reproduction Update. 2011 Sep 1;17(5):589–604.	NA
Offspring					
Offspring Congenital Rubella	ICD-10 diagnosis for the offspring	S: Medical Birth Registry; N: National	Literature	Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 Spring;40(2):99–114.	Table 34

ANNEX 3F. POTENTIAL RISK FACTORS CODELISTS for CM					
	between birth and exit date; binary yes/no	Patient/Hospital Registry; D: National Patient Registry			
Offspring Congenital Varicella	ICD-10 diagnosis for the offspring between birth and exit date; binary yes/no	Medical Birth Registry	Literature	1) Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 Spring;40(2):99–114. 2) Ferry T, Vial Y, Vaudaux B. [Varicella during pregnancy: consequences for the mother and the newborn]. Rev Med Suisse. 2011 Apr 27;7(292):900–4.	Table 36
Offspring Congenital CMV	ICD-10 diagnosis for the offspring between birth and exit date; binary yes/no	Medical Birth Registry	Literature	Lanzieri TM, Leung J, Caviness AC, Chung W, Flores M, Blum P, et al. Long-term outcomes of children with symptomatic congenital cytomegalovirus disease. J Perinatol. 2017 Jul;37(7):875–80.	Table 32
Offspring Congenital Herpes Simplex Viral Infections	ICD-10 diagnosis for the offspring between birth and exit date; binary yes/no	Medical Birth Registry	Literature	Ferry T, Vial Y, Vaudaux B. [Varicella during pregnancy: consequences for the mother and the newborn]. Rev Med Suisse. 2011 Apr 27;7(292):900–4.	Table 33
Offspring Congenital Toxoplasmosis	ICD-10 diagnosis for the offspring between birth and exit date; binary yes/no	Medical Birth Registry	Literature	Gilbert-Barness E. Teratogenic causes of malformations. Ann Clin Lab Sci. 2010 Spring;40(2):99–114.	Table 35
Offspring Foetal Alcohol Syndrome	ICD-10 diagnosis for the offspring between birth	S: Medical Birth Registry; N: National Patient/Hospital Registry; D:	Literature	1)Mesquita M dos A, Segre CA de M, Mesquita M dos A, Segre CA de M. Congenital malformations in newborns of alcoholic mothers. Einstein (São Paulo). 2010 Dec;8(4):461–6. 2)Grewal J, Carmichael SL, Ma C, Lammer EJ, Shaw GM. Maternal Periconceptional Smoking and Alcohol Consumption and Risk for Select	Table 38

ANNEX 3F. POTENTIAL RISK FACTORS CODELISTS for CM					
	and exit date; binary yes/no	National Patient Registry		Congenital Anomalies. Birth Defects Res A Clin Mol Teratol. 2008 Jul;82(7):519–26. 3)Riley EP, Infante MA, Warren KR. Fetal Alcohol Spectrum Disorders: An Overview. Neuropsychol Rev. 2011 Jun;21(2):73–80.	

ATC: Anatomical Therapeutic Chemical; CMV: Cytomegalovirus; DP: during pregnancy; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; LMP2: Last Menstrual Period + 2 weeks; S: Sweden; N: Norway; D: Denmark; NA: Not Applicable; WHO: World Health Organization.

Annex 3G - Codelists

Table 8: ASD

ICD 10	Clinical Code Description
F840	Childhood autism
F841	Atypical autism
F842	Rett's syndrome
F843	Other childhood disintegrative disorder
F845	Asperger syndrome
F848	Other pervasive developmental disorders
F849	Pervasive developmental disorder, unspecified

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 9: NDD excluding ASD

ICD 10	Clinical Code Description	Category
F70	Intellectual Disability - Mild	Intellectual disabilities
F71	Intellectual Disability - Moderate	
F72	Intellectual Disability - Severe	
F73	Intellectual Disability - Profound	
F78	Other Intellectual Disability	
F79	Unspecified Intellectual Disability	
F80	Specific developmental disorders of speech and language	Communication disorders
F81	Specific developmental disorders of scholastic skills	Disorders of psychological development
F83	Mixed specific developmental delays	
F84.4	Overactive disorder associated with mental retardation and stereotyped movements	
F88	Other disorders of psychological development	
F89	Unspecified disorder of psychological development	
F99	Mental disorder, not otherwise specified	
R48	Dyslexia and other symbolic dysfunctions, not elsewhere classified	
F90	Hyperkinetic disorders	Hyperkinetic disorders
F988	Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	

ICD 10	Clinical Code Description	Category
F95	Tic disorders	Tic Disorders
F82	Specific developmental disorder of motor function	Movement disorders
F984	Stereotyped movement disorders	
G250	Essential tremor	
G252	Other specified forms of tremor	
G253	Myoclonus	
G255	Other chorea	
G258	Other specified extrapyramidal and movement disorders	
G259	Extrapyramidal and movement disorder, unspecified	
G242 G243 G244 G245 G248 G249	Idiopathic nonfamilial dystonia Spasmodic torticollis Idiopathic orofacial dystonia Blepharospasm Other dystonia Dystonia, unspecified	
G26	Extrapyramidal and movement disorders in diseases classified elsewhere	

ASD: Autism Spectrum Disorder; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; NDD: Neurodevelopmental disorders.

Table 10: NDD all

ICD 10	Clinical Code Description	Category
F70	Intellectual Disability - Mild	Intellectual disabilities
F71	Intellectual Disability - Moderate	
F72	Intellectual Disability - Severe	
F73	Intellectual Disability - Profound	
F78	Other Intellectual Disability	
F79	Unspecified Intellectual Disability	
F80	Specific developmental disorders of speech and language	Communication disorders
F81	Specific developmental disorders of scholastic skills	Disorders of psychological development
F83	Mixed specific developmental delays	
F84	Pervasive developmental disorders	
F88	Other disorders of psychological development	
F89	Unspecified disorder of psychological development	
F99	Mental disorder, not otherwise specified	
R48	Dyslexia and other symbolic dysfunctions, not elsewhere classified	
F90	Hyperkinetic disorders	Hyperkinetic disorders
F988	Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	
F95	Tic disorders	Tic Disorders
F82	Specific developmental disorder of motor function	Movement disorders
F984	Stereotyped movement disorders	
G250	Essential tremor	
G252	Other specified forms of tremor	
G253	Myoclonus	
G255	Other chorea	
G258	Other specified extrapyramidal and movement disorders	
G259	Extrapyramidal and movement disorder, unspecified	

ICD 10	Clinical Code Description	Category
G242 G243 G244 G245 G248 G249	Idiopathic nonfamilial dystonia Spasmodic torticollis Idiopathic orofacial dystonia Blepharospasm Other dystonia Dystonia, unspecified	
G26	Extrapyramidal and movement disorders in diseases classified elsewhere	

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; NDD: Neurodevelopmental disorders.

Table 11: CM all

Subgroups	ICD 10 - major	MAJOR-specific exclusions	ICD 10 - minor	MINOR-specific exclusions
Nervous System	Q00 Q01 Q02 Q03 Q04 Q05 Q06 Q07			-
Eye	Q10 Q11 Q12 Q13 Q14 Q15		Q101 Q102 Q103 Q105 Q135 Q752	
Ear, face, and neck	Q16 Q17 Q18		Q170 Q171 Q172 Q173 Q174 Q175 Q179 Q180 Q181 Q182 Q184 Q185 Q186 Q187 Q189	
Congenital Heart Defects	Q20 Q21 Q22 Q23 Q24 Q25 Q26	Q250 if: -non-live birth -live birth with gestational age is <37 weeks Q270"	Q270 Q250	Q250 if: -non-live birth -live birth with gestational age is >37 weeks
Respiratory	Q30 Q31 Q32 Q33 Q34		Q315 Q320 Q331 Q309	

Subgroups	ICD 10 - major	MAJOR-specific exclusions	ICD 10 - minor	MINOR-specific exclusions
Oro-facial	Q35 Q36 Q37	If codes Q35-Q37 co-occur with codes Q00 or Q041 or Q042 classify record under 'Nervous System' subgroup		
Digestive system	Q38 Q39 Q40 Q41 Q42 Q43 Q44 Q45 Q790		Q381 Q382 Q400 Q401 Q430	
Abdominal wall defects	Q792 Q793 Q795			
Urinary	Q60 Q61 Q62 Q63 Q64		Q610 Q627 Q633	
Genital	Q50 Q51 Q52 Q54 Q55 Q56		Q523 Q525 Q540	

Subgroups	ICD 10 - major	MAJOR-specific exclusions	ICD 10 - minor	MINOR-specific exclusions
Limb	Q65 Q66 Q69 Q70 Q71 Q72 Q73 Q74		Q653 Q654 Q655 Q656 Q662 Q663 Q664 Q665 Q666 Q667 Q668 Q669 Q845	
Chromosomal	Q90 Q91 Q92 Q93 Q96 Q97 Q98 Q99	Q936	Q950 Q951	
Musculo-skeletal	Q67 Q68 Q77 Q782 Q783 Q784 Q785 Q786 Q787 Q788		Q680 Q672 Q673 Q753 Q670 Q671 Q674 Q677 Q676 Q678 Q675 Q683 Q684 Q685 Q760 Q765	
Craniosynostosis	Q750			
Situs inversus	Q893			
Conjoined twins	Q894			
Congenital skin disorders	Q80 Q81 Q82		Q825 Q833	

Subgroups	ICD 10 - major	MAJOR-specific exclusions	ICD 10 - minor	MINOR-specific exclusions
Genetic syndromes + microdeletions	Q751 Q754 Q87 Q936 D821			
Genetic syndromes + sequences	Q606 Q794			

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.
List excludes teratogenic syndromes, foetal alcohol syndrome and maternal infections causing malformations.

Table 12: CM major

Subgroups	ICD 10 -major	ICD 10 -minor (EXCLUDE)	Other exclusions
Nervous System	Q00 Q01 Q02 Q03 Q04 Q05 Q06 Q07		
Eye	Q10 Q11 Q12 Q13 Q14 Q15	Q101 Q102 Q103 Q105 Q135 Q752	
Ear, face, and neck	Q16 Q17 Q18	Q170 Q171 Q172 Q173 Q174 Q175 Q179 Q180 Q181 Q182 Q184 Q185 Q186 Q187 Q189	

Subgroups	ICD 10 -major	ICD 10 -minor (EXCLUDE)	Other exclusions
Congenital Heart Defects	Q20 Q21 Q22 Q23 Q24 Q25 Q26	Q250 if: -non-live birth -live birth with gestational age is <37 weeks Q270	
Respiratory	Q30 Q31 Q32 Q33 Q34	Q315 Q320 Q331 Q309	
Oro-facial	Q35 Q36 Q37		If codes Q35-Q37 co-occur with codes Q00 or Q041 or Q042 classify record under 'Nervous System' subgroup
Digestive system	Q38 Q39 Q40 Q41 Q42 Q43 Q44 Q45 Q790	Q381 Q382 Q400 Q401 Q430	
Abdominal wall defects	Q792 Q793 Q795		
Urinary	Q60 Q61 Q62 Q63 Q64	Q610 Q627 Q633	
Genital	Q50 Q51 Q52 Q54 Q55 Q56	Q523 Q525 Q540	

Subgroups	ICD 10 -major	ICD 10 -minor (EXCLUDE)	Other exclusions
Limb	Q65 Q66 Q69 Q70 Q71 Q72 Q73 Q74	Q653 Q654 Q655 Q656 Q662 Q663 Q664 Q665 Q666 Q667 Q668 Q669 Q845	
Chromosomal	Q90 Q91 Q92 Q93 Q96 Q97 Q98 Q99	Q950 Q951	Q936
Musculo-skeletal	Q67 Q68 Q77 Q782 Q783 Q784 Q785 Q786 Q787 Q788	Q680 Q672 Q673 Q753 Q677 Q676 Q678 Q675 Q683 Q684 Q685 Q760 Q765 Q670 Q671 Q674	
Craniosynostosis	Q750		
Situs inversus	Q893		
Conjoined twins	Q894		
Congenital skin disorders	Q80 Q81 Q82	Q825 Q833	

Subgroups	ICD 10 -major	ICD 10 -minor (EXCLUDE)	Other exclusions
Genetic syndromes + microdeletions	Q751 Q754 Q87 Q936 D821		
Genetic syndromes + sequences	Q606 Q794		

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.
List excludes teratogenic syndromes, foetal alcohol syndrome and maternal infections causing malformations.

Table 13: CM minor

Subgroups	ICD 10	Exclusions
Eye	Q101 Q102 Q103 Q105 Q135 Q752	
Ear, face, and neck	Q170 Q171 Q172 Q173 Q174 Q175 Q179 Q180 Q181 Q182 Q184 Q185 Q186 Q187 Q189	
Congenital Heart Defects	Q250 if: -non-live birth -live birth with gestational age is <37 weeks Q270	Q250 if: -non-live birth -live birth with gestational age is >37 weeks
Respiratory	Q315 Q320 Q331 Q309	
Digestive system	Q381 Q382 Q400 Q401 Q430	
Urinary	Q610 Q627 Q633	
Genital	Q523 Q525 Q540	

Subgroups	ICD 10	Exclusions
Limb	Q653 Q654 Q655 Q656 Q662 Q663 Q664 Q665 Q666 Q667 Q668 Q669 Q845	
Chromosomal	Q950 Q951	
Musculo-skeletal	Q680 Q672 Q673 Q753 Q677 Q676 Q678 Q675 Q683 Q684 Q685 Q760 Q765 Q670 Q671 Q674	
Congenital skin disorders	Q825 Q833	

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.
List excludes teratogenic syndromes, foetal alcohol syndrome and maternal infections causing malformations.

Table 14: Study drugs

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AG01	Valproate (valproic acid)	Fatty Acid derivatives
N03AG02	Valproate (valpromide)	Fatty Acid derivatives
N03AX09	Lamotrigine	Other Antiepileptics
N03AX14	Levetiracetam	Other Antiepileptics

ATC: Anatomical Therapeutic Chemical.

Table 15: Lamotrigine

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AX09	Lamotrigine	Other Antiepileptics

ATC: Anatomical Therapeutic Chemical.

Table 16: Levetiracetam

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AX14	Levetiracetam	Other Antiepileptics

ATC: Anatomical Therapeutic Chemical.

Table 17: Valproate

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AG01	Valproate (valproic acid)	Fatty Acid derivatives
N03AG02	Valproate (valpromide)	Fatty Acid derivatives

ATC: Anatomical Therapeutic Chemical.

Table 18: Bipolar

ICD 10	Clinical Code Description
F25	Schizoaffective disorder
F31	Bipolar Affective Disorder

ICD 10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 19: Epilepsy

ICD 10	Clinical Code Description
G40	Epilepsy and recurrent seizures

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 20: Mania

ICD 10	Clinical Code Description
F30	Manic episode

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 21: Intrauterine Growth Restriction- IGR

ICD 10	Clinical Code Description
O36.5	Maternal care for poor foetal growth
P05.0	Light for gestational age
P05.1	Small for gestational age
P05.9	Slow foetal growth, unspecified
P07.0	Extremely low birth weight
P07.1	Other low birth weight

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 22: Perinatal mortality

ICD 10	Clinical Code Description
P95	Still birth
Z371	Single Stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.7	Other multiple births, all stillborn
Z37.6	Other multiple births, some liveborn

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 23: Live birth

ICD 10	Clinical Code Description
Z37.0	Single live birth
Z37.2	Twins, both liveborn
Z37.5	Other multiple births, all liveborn
Z38	Liveborn infants according to place of birth

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 24: Non-live birth

ICD 10	Clinical Code Description
P95	Still birth
Z371	Single Stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.7	Other multiple births, all stillborn
O312	Continuing pregnancy after intrauterine death one foetus or more
O36.4	Maternal care for intrauterine death
O021	Missed Abortion
O03	Spontaneous Abortion
O311	Continuing pregnancy after abortion of one foetus or more
Z37.6	Other multiple births, some liveborn

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 25: Spontaneous abortion

ICD 10	Clinical Code Description
O021	Missed Abortion
O03	Spontaneous Abortion
O311	Continuing pregnancy after abortion of one foetus or more

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 26: Stillbirth

ICD 10	Clinical Code Description
P95	Still birth
Z371	Single Stillbirth
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.7	Other multiple births, all stillborn
O312	Continuing pregnancy after intrauterine death one foetus or more
O36.4	Maternal care for intrauterine death
Z37.6	Other multiple births, some liveborn

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 27: Affective disorder

ICD 10	Clinical Code Description
F30	Manic episode
F31	Bipolar disorder
F32	Major depressive disorder, single episode
F33	Major depressive disorder, recurrent
F34	Persistent mood [affective] disorders
F38	Other mood [affective] disorders
F39	Unspecified mood [affective] disorder

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 28: Affective disorder excluding bipolar mania

ICD 10	Clinical Code Description
F32	Major depressive disorder, single episode
F33	Major depressive disorder, recurrent
F34	Persistent mood [affective] disorders
F38	Other mood [affective] disorders
F39	Unspecified mood [affective] disorder

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 29: Alcohol – during pregnancy

ICD 10	Clinical Code Description
F101	Alcohol-Harmful use
F103	Alcohol-Withdrawal state
F104	Alcohol-Withdrawal with delirium
K292	Alcoholic gastritis
O354	Maternal care for (suspected) damage to foetus from alcohol
P043	Foetus and newborn affected by maternal use of alcohol
Q860	Foetal alcohol syndrome

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 30: Alcohol

ICD 10	Clinical Code Description
F10	Alcohol abuse
K292	Alcoholic gastritis
K701	Alcoholic hepatitis
K702	Alcoholic fibrosis and sclerosis of liver
K703	Alcoholic cirrhosis of liver
K704	Alcoholic hepatic failure
K709	Alcoholic liver disease, unspecified
Z714	Alcohol abuse counselling and surveillance
I426	Alcoholic cardiomyopathy
G621	Alcoholic polyneuropathy
G721	Alcoholic myopathy
G312	Degeneration of nervous system due to alcohol
O354	Maternal care for (suspected) damage to foetus from alcohol

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 31: CMV

ICD 10	Clinical Code Description
B25	Cytomegaloviral disease
B271	Cytomegaloviral mononucleosis
B202	HIV disease resulting in cytomegaloviral disease

HIV: human immunodeficiency virus; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision, CMV: Cytomegalovirus.

Table 32: CMV congenital

ICD 10	Clinical Code Description
B271	Cytomegaloviral mononucleosis
B25	Cytomegaloviral disease
P35.1	Congenital cytomegalovirus infection

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision, CMV: Cytomegalovirus.

Table 33: Herpes simplex congenital

ICD 10	Clinical Code Description
P352	Congenital herpesvirus [herpes simplex] infection
B00	Herpesviral [herpes simplex] infections
H191	Herpesviral keratitis and keratoconjunctivitis

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 34: Rubella congenital

ICD 10	Clinical Code Description
P350	Congenital rubella syndrome
B06	Rubella

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 35: Toxoplasmosis congenital

ICD 10	Clinical Code Description
P371	Congenital toxoplasmosis
B58	Toxoplasmosis

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 36: Varicella congenital

ICD 10	Clinical Code Description
B01	Varicella [chickenpox]
B02	Zoster [herpes zoster]

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 37: Diabetes

ICD 10	Clinical Code Description
E10	Type 1 diabetes mellitus/Insulin-dependent
E11	Type 2 diabetes mellitus/non-insulin-dependent
E08	Diabetes mellitus due to underlying condition
E09	Drug or chemical induced diabetes mellitus
E14	Unspecified diabetes mellitus
E13	Other specified diabetes mellitus
P701	Syndrome of infant of a diabetic mother

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 38: Foetal alcohol syndrome

ICD 10	Clinical Code Description
Q860	Foetal alcohol syndrome (dysmorphic)
P043	Alcohol affecting foetus or newborn via placenta or breast milk
O354	Maternal care for (suspected) damage to foetus from alcohol, other foetus

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 39: Folate deficiency

ICD 10	Clinical Code Description
D52	Folate Deficiency Anaemia

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 40: Fragile syndrome

ICD 10	Clinical Code Description
Q992	Fragile X Chromosome

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 41: Gestational diabetes

ICD 10	Clinical Code Description
O24	Diabetes mellitus in pregnancy, childbirth, and the puerperium
P700	Syndrome of infant of mother with gestational diabetes

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 42: Herpes simplex

ICD 10	Clinical Code Description
B00	Herpesviral [herpes simplex] infections
A60	Anogenital herpesviral [herpes simplex] infections
O264	Herpes gestations
H191	Herpesviral keratitis and keratoconjunctivitis

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 43: Lejeune cri du chat syndrome

ICD 10	Clinical Code Description
Q934	Deletion of short arm of chromosome 5

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 44: Neurotic disorder

ICD 10	Clinical Code Description
F40	Phobic anxiety disorders
F41	Other anxiety disorders
F42	Obsessive-compulsive disorder
F43	Reaction to severe stress, and adjustment disorders
F44	Dissociative and conversion disorders
F45	Somatoform disorders
F48	Other neurotic disorders

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 45: Obesity

ICD 10	Clinical Code Description
E66	Obesity

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 46: Rubella

ICD 10	Clinical Code Description
B06	Rubella

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 47: Schizophrenia

ICD 10	Clinical Code Description
F20	Schizophrenia
F21	Schizotypal disorder
F22	Persistent delusional disorders
F23	Acute and transient psychotic disorders
F24	Induced delusional disorder
F28	Other nonorganic psychotic disorders
F29	Unspecified nonorganic psychosis

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 48: Substance – during pregnancy

ICD 10	Clinical Code Description
F111 F113 F114	Opioid related disorders- harmful use, withdrawal, withdrawal and delirium
F121 F123 F124	Cannabis related disorders- harmful use, withdrawal, withdrawal and delirium
F131 F133 F134	Sedative, hypnotic, or anxiolytic related disorders - harmful use, withdrawal, withdrawal and delirium
F141 F143 F144	Cocaine related disorders - harmful use, withdrawal, withdrawal and delirium
F161 F163 F164	Hallucinogen related disorders - harmful use, withdrawal, withdrawal and delirium
F181 F183 F184	Inhalant related disorders - harmful use, withdrawal, withdrawal and delirium
P044	Fetus and newborn affected by maternal use of drugs of addiction
P961	Neonatal withdrawal symptom from maternal use of drug of addiction

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 49: Substance

ICD 10	Clinical Code Description
F11	Opioid related disorders
F12	Cannabis related disorders
F13	Sedative, hypnotic, or anxiolytic related disorders
F14	Cocaine related disorders
F16	Hallucinogen related disorders
F18	Inhalant related disorders
Z715	Drug abuse counselling and surveillance
P044	Fetus and newborn affected by maternal use of drugs of addiction
P961	Neonatal withdrawal symptom from maternal use of drug of addiction

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 50: Toxoplasmosis

ICD 10	Clinical Code Description
B58	Toxoplasmosis

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 51: Tuberous sclerosis

ICD 10	Clinical Code Description
Q851	Tuberous Sclerosis

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 52: Varicella

ICD 10	Clinical Code Description
B01	Varicella [chickenpox]
B02	Zoster [herpes zoster]

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 53: Multiple pregnancny

ICD 10	Clinical Code Description
Z37.3	Twins, one liveborn and one stillborn
Z37.4	Twins, both stillborn
Z37.7	Other multiple births, all stillborn
O30	Multiple gestation
O31	Complications specific to multiple gestation
O32.5	Maternal care for multiple gestation with malpresentation of one foetus or more
P01.5	foetus and newborn affected by multiple pregnancy
Z38.3	Twin, born in hospital
Z38.4	Twin, born outside hospital
Z38.5	Twin, unspecified as to place of birth
Z38.6	Other multiple, born in hospital
Z38.7	Other multiple, born outside hospital
Z38.8	Other multiple, unspecified as to place of birth
O66.1	Obstructed labour due to locked twins

ICD 10	Clinical Code Description
Q89.4	Conjoined twins
O63.2	Delayed delivery of second twin, triplet, etc.
P50.5	Foetal blood loss from cut end of co-twin's cord
P50.3	Haemorrhage into co-twin
Z37.2	Twins, both liveborn
Z37.6	Other multiple births, some stillborn
Z37.5	Other multiple births, all liveborn
O84	Multiple delivery

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revisions.

Table 54: Concomitant medicines to neuropsychiatric adverse event

ATC code	Name (5th level ATC, chemical substance)
A02BC02	Pantoprazole
A02BC05	Esomeprazole
A02BD01	omeprazole, amoxicillin and metronidazole
A02BD02	lansoprazole, tetracycline and metronidazole
A02BD03	lansoprazole, amoxicillin and metronidazole
A02BD04	pantoprazole, amoxicillin and clarithromycin
A02BD05	omeprazole, amoxicillin and clarithromycin
A02BD06	esomeprazole, amoxicillin and clarithromycin
A02BD07	lansoprazole, amoxicillin and clarithromycin
A02BD08	bismuth subcitrate, tetracycline and metronidazole
A02BD09	lansoprazole, clarithromycin and tinidazole
A02BD10	lansoprazole, amoxicillin and levofloxacin
A02BD11	pantoprazole, amoxicillin, clarithromycin and metronidazole
A02BD12	rabeprazole, amoxicillin and clarithromycin
A02BD13	rabeprazole, amoxicillin and metronidazole
A02BD14	vonoprazan, amoxicillin and clarithromycin
A02BD15	vonoprazan, amoxicillin and metronidazole
A03AB02	Glycopyrronium
A04AA02	Granisetron
A04AA05	Palonosetron

ATC code	Name (5th level ATC, chemical substance)
A04AA55	Palonosetron, combinations
A04AD12	Aprepitant
A04AD14	Rolapitant
A05AA03	Cholic acid
A05AA04	Obeticholic acid
A06AH01	Methylnaltrexone bromide
A06AH03	Naloxegol
A06AX04	Linaclotide
A06AX05	Prucalopride
A07AA12	Fidaxomicin
A07DA06	Eluxadoline
A08AA01	phentermine
A08AA02	fenfluramine
A08AA03	amfepramone
A08AA04	dexfenfluramine
A08AA05	mazindol
A08AA06	etilamfetamine
A08AA07	cathine
A08AA08	clobenzorex
A08AA09	mefenorex
A08AA10	sibutramine
A08AA11	lorcaserin
A08AA56	ephedrine, combinations
A08AA62	bupropion and naltrexone
A08AB01	Orlistat
A09AA02	Pancreatin
A10AB01	Insulin human
A10AB05	Insulin aspart
A10AC01	Insulin human
A10AD01	Insulin human
A10AD05	Insulin aspart
A10AE04	Insulin glargine

ATC code	Name (5th level ATC, chemical substance)
A10AE05	Insulin detemir
A10AE54	Insulin glargine, lixisenatide
A10BD05	Pioglitazone, metformin
A10BD06	Glimepiride, pioglitazone
A10BD07	Metformin, sitagliptin
A10BD08	Vildagliptin, metformin
A10BD09	Pioglitazone, alogliptin
A10BD10	Metformin, saxagliptin
A10BD11	Metformin hydrochloride, linagliptin
A10BD13	Metformin, alogliptin
A10BD15	Metformin, dapagliflozin
A10BD16	Metformin, canagliflozin
A10BD20	Metformin, empagliflozin
A10BD21	Saxagliptin, dapagliflozin
A10BG03	Pioglitazone
A10BH01	Sitagliptin
A10BH02	Vildagliptin
A10BH03	Saxagliptin
A10BH04	Alogliptin
A10BJ01	Exenatide
A10BJ02	Liraglutide
A10BJ03	Lixisenatide
A10BK01	Dapagliflozin
A10BK02	Canagliflozin
A10BK03	Empagliflozin
A10BX02	Repaglinide
A10BX03	Nateglinide
A11HA08	Tocofersolan
A14AA01	androstanolone
A14AA02	stanozolol
A14AA03	metandienone
A14AA04	metenolone

ATC code	Name (5th level ATC, chemical substance)
A14AA05	oxymetholone
A14AA06	quinbolone
A14AA07	prasterone
A14AA08	oxandrolone
A14AA09	norethandrolone
A14AB01	nandrolone
A14AB02	ethylestrenol
A14AB03	oxabolone cipionate
A16AA04	Mercaptamine
A16AA06	Betaine
A16AB02	Imiglucerase
A16AB03	Agalsidase alfa
A16AB04	Agalsidase beta
A16AB05	Laronidase
A16AB07	Alglucosidase alfa
A16AB08	Galsulfase
A16AB09	Idursulfase
A16AB10	Velaglucerase alfa
A16AB12	Elosulfase alfa
A16AB13	Asfotase alfa
A16AB14	Sebelipase alfa
A16AB17	Cerliponase alfa
A16AX03	Sodium phenylbutyrate
A16AX06	Miglustat
A16AX07	Sapropterin
A16AX08	Teduglutide
A16AX09	Glycerol phenylbutyrate
A16AX10	Eliglustat
A16AX14	Migalastat
B01AB02	Antithrombin alfa
B01AB05	Enoxaparin
B01AC04	Clopidogrel

ATC code	Name (5th level ATC, chemical substance)
B01AC11	Iloprost
B01AC16	Eptifibatide
B01AC22	Prasugrel
B01AC24	Ticagrelor
B01AC25	Cangrelor
B01AC27	Selexipag
B01AC30	Clopidogrel, acetylsalicylic acid
B01AD08	Reteplase
B01AD11	Tenecteplase
B01AD12	Protein c
B01AE06	Bivalirudin
B01AE07	Dabigatran
B01AF01	Rivaroxaban
B01AF02	Apixaban
B01AF03	Edoxaban
B01AX01	Defibrotide
B01AX05	Fondaparinux
B02AB02	Human alpha1-proteinase inhibitor
B02BC01	absorbable gelatin sponge
B02BC02	oxidized cellulose
B02BC03	tetragalacturonic acid hydroxymethylester
B02BC05	adrenalone
B02BC06	thrombin
B02BC07	collagen
B02BC08	calcium alginate
B02BC09	epinephrine
B02BC30	combinations
B02BD02	Coagulation factor IX
B02BD04	Coagulation factor VIII
B02BD06	Human coagulation factor viii, human von willebrand factor
B02BD08	Eptacog alfa
B02BD11	Catridecacog

ATC code	Name (5th level ATC, chemical substance)
B02BD13	Human coagulation factor x
B02BD14	Susoctocog alfa
B02BX04	Romiplostim
B02BX05	Eltrombopag
B03XA01	Epoetin alfa
B03XA02	Darbepoetin alfa
B03XA03	Methoxy polyethylene glycol-epoetin beta
B06AC01	Complement c1 esterase inhibitor
B06AC02	Icatibant
B06AC04	Conestat alfa
C01AA01	acetyldigitoxin
C01AA02	acetyldigoxin
C01AA03	digitalis leaves
C01AA04	digitoxin
C01AA05	digoxin
C01AA06	lanatoside C
C01AA07	deslanoside
C01AA08	metildigoxin
C01AA09	gitoformate
C01AA52	acetyldigoxin, combinations
C01BA01	quinidine
C01BA02	procainamide
C01BA03	disopyramide
C01BA04	sparteine
C01BA05	ajmaline
C01BA08	prajmaline
C01BA12	lorajmine
C01BA13	hydroquinidine
C01BA51	quinidine, combinations excl. psycholeptics
C01BA71	quinidine, combinations with psycholeptics
C01BB01	lidocaine
C01BB02	mexiletine

ATC code	Name (5th level ATC, chemical substance)
C01BB03	tocainide
C01BB04	aprindine
C01BC03	propafenone
C01BC04	flecainide
C01BC07	lorcainide
C01BC08	encainide
C01BC09	ethacizine
C01BD01	amiodarone
C01BD02	bretylium tosilate
C01BD03	bunaftine
C01BD04	dofetilide
C01BD05	ibutilide
C01BD06	tedisamil
C01BD07	dronedarone
C01BG01	moracizine
C01BG07	cibenzoline
C01BG11	vernakalant
C01DA02	glyceryl trinitrate
C01DA04	methylpropylpropanediol dinitrate
C01DA05	pentaerithrityl tetranitrate
C01DA07	propatylnitrate
C01DA08	isosorbide dinitrate
C01DA09	trolnitrate
C01DA13	erityrityl tetranitrate
C01DA14	isosorbide mononitrate
C01DA20	organic nitrates in combination
C01DA38	tenitramine
C01DA52	glyceryl trinitrate, combinations
C01DA54	methylpropylpropanediol dinitrate, combinations
C01DA55	pentaerithrityl tetranitrate, combinations
C01DA57	propatylnitrate, combinations
C01DA58	isosorbide dinitrate, combinations

ATC code	Name (5th level ATC, chemical substance)
C01DA59	trolnitrate, combinations
C01DA63	erityl tetranitrate, combinations
C01DA70	organic nitrates in combination with psycholeptics
C01DB01	flosequinan
C01DX01	itramin tosilate
C01DX02	prenylamine
C01DX03	oxyfedrine
C01DX04	benziodarone
C01DX05	carbocromen
C01DX06	hexobendine
C01DX07	etafenone
C01DX08	heptaminol
C01DX09	imolamine
C01DX10	dilazep
C01DX11	trapidil
C01DX12	molsidomine
C01DX13	efloxate
C01DX14	cinepazet
C01DX15	cloridarol
C01DX16	nicorandil
C01DX18	linsidomine
C01DX19	nesiritide
C01DX21	serelaxin
C01DX51	itramin tosilate, combinations
C01DX52	prenylamine, combinations
C01DX53	oxyfedrine, combinations
C01DX54	benziodarone, combinations
C01EB17	Ivabradine
C01EB18	Ranolazine
C01EB21	Regadenoson
C02AC02	Guanfacine
C02CA01	prazosin

ATC code	Name (5th level ATC, chemical substance)
C02CA02	indoramin
C02CA03	trimazosin
C02CA04	doxazosin
C02CA06	urapidil
C02CC01	betanidine
C02CC02	guanethidine
C02CC03	guanoxan
C02CC04	debrisoquine
C02CC05	guanoclor
C02CC06	guanazodine
C02CC07	guanoxabenz
C02KX01	Bosentan
C02KX02	Ambrisentan
C02KX04	Macitentan
C02KX05	Riociguat
C02LA01	reserpine and diuretics
C02LA02	rescinnamine and diuretics
C02LA03	deserpidine and diuretics
C02LA04	methoserpidine and diuretics
C02LA07	bietaserpine and diuretics
C02LA08	rauwolfia alkaloids, whole root and diuretics
C02LA09	syrosingopine and diuretics
C02LA50	combination of rauwolfia alkaloids and diuretics incl. other combinations
C02LA51	reserpine and diuretics, combinations with other drugs
C02LA52	rescinnamine and diuretics, combinations with other drugs
C02LA71	reserpine and diuretics, combinations with psycholeptics
C02LB01	methyldopa (levorotatory) and diuretics
C02LC01	clonidine and diuretics
C02LC05	moxonidine and diuretics
C02LC51	clonidine and diuretics, combinations with other drugs
C02LE01	prazosin and diuretics
C02LF01	guanethidine and diuretics

ATC code	Name (5th level ATC, chemical substance)
C02LG01	dihydralazine and diuretics
C02LG02	hydralazine and diuretics
C02LG03	picodralazine and diuretics
C02LG51	dihydralazine and diuretics, combinations with other drugs
C02LG73	picodralazine and diuretics, combinations with psycholeptics
C02LK01	veratrum and diuretics
C02LL01	pargyline and diuretics
C02LX01	pinacidil and diuretics
C03AA01	bendroflumethiazide
C03AA02	hydroflumethiazide
C03AA03	hydrochlorothiazide
C03AA04	chlorothiazide
C03AA05	polythiazide
C03AA06	trichlormethiazide
C03AA07	cyclopenthiazide
C03AA08	methyclothiazide
C03AA09	cyclothiazide
C03AA13	mebutizide
C03AB01	bendroflumethiazide and potassium
C03AB02	hydroflumethiazide and potassium
C03AB03	hydrochlorothiazide and potassium
C03AB04	chlorothiazide and potassium
C03AB05	polythiazide and potassium
C03AB06	trichlormethiazide and potassium
C03AB07	cyclopenthiazide and potassium
C03AB08	methyclothiazide and potassium
C03AB09	cyclothiazide and potassium
C03AH01	chlorothiazide, combinations
C03AH02	hydroflumethiazide, combinations
C03AX01	hydrochlorothiazide, combinations
C03EA01	hydrochlorothiazide and potassium-sparing agents
C03EA02	trichlormethiazide and potassium-sparing agents

ATC code	Name (5th level ATC, chemical substance)
C03EA03	epitizide and potassium-sparing agents
C03EA04	altizide and potassium-sparing agents
C03EA05	mebutizide and potassium-sparing agents
C03EA06	chlortalidone and potassium-sparing agents
C03EA07	cyclopenthiazide and potassium-sparing agents
C03EA12	metolazone and potassium-sparing agents
C03EA13	bendroflumethiazide and potassium-sparing agents
C03EA14	butizide and potassium-sparing agents
C03EB01	furosemide and potassium-sparing agents
C03EB02	bumetanide and potassium-sparing agents
C03XA01	Tolvaptan
C07AA01	alprenolol
C07AA02	oxprenolol
C07AA03	pindolol
C07AA05	propranolol
C07AA06	timolol
C07AA07	sotalol
C07AA12	nadolol
C07AA14	mepindolol
C07AA15	carteolol
C07AA16	tertatolol
C07AA17	bopindolol
C07AA19	bupranolol
C07AA23	penbutolol
C07AA27	cloranolol
C07AB01	practolol
C07AB02	metoprolol
C07AB03	atenolol
C07AB04	acebutolol
C07AB05	betaxolol
C07AB06	bevantolol
C07AB07	bisoprolol

ATC code	Name (5th level ATC, chemical substance)
C07AB08	celiprolol
C07AB09	esmolol
C07AB10	epanolol
C07AB11	s-atenolol
C07AB12	nebivolol
C07AB13	talinolol
C07AB14	landiolol
C07AG01	labetalol
C07AG02	carvedilol
C08CA01	amlodipine
C08CA02	felodipine
C08CA03	isradipine
C08CA04	nicardipine
C08CA05	nifedipine
C08CA06	nimodipine
C08CA07	nisoldipine
C08CA08	nitrendipine
C08CA09	lacidipine
C08CA10	nilvadipine
C08CA11	manidipine
C08CA12	barnidipine
C08CA13	lercanidipine
C08CA14	cilnidipine
C08CA15	benidipine
C08CA16	clevidipine
C08CA51	amlodipine and celecoxib
C08CA55	nifedipine, combinations
C08CX01	mibefradil
C08DA01	verapamil
C08DA02	gallopamil
C08DA51	verapamil, combinations
C08DB01	diltiazem

ATC code	Name (5th level ATC, chemical substance)
C08EA01	fendiline
C08EA02	bepridil
C08EX01	lidoflazine
C08EX02	perhexiline
C08GA01	nifedipine and diuretics
C08GA02	amlodipine and diuretics
C09AA01	captopril
C09AA02	enalapril
C09AA03	lisinopril
C09AA04	perindopril
C09AA05	ramipril
C09AA06	quinapril
C09AA07	benazepril
C09AA08	cilazapril
C09AA09	fosinopril
C09AA10	trandolapril
C09AA11	spirapril
C09AA12	delapril
C09AA13	moexipril
C09AA14	temocapril
C09AA15	zofenopril
C09AA16	imidapril
C09BA01	captopril and diuretics
C09BA02	enalapril and diuretics
C09BA03	lisinopril and diuretics
C09BA04	perindopril and diuretics
C09BA05	ramipril and diuretics
C09BA06	quinapril and diuretics
C09BA07	benazepril and diuretics
C09BA08	cilazapril and diuretics
C09BA09	fosinopril and diuretics
C09BA12	delapril and diuretics

ATC code	Name (5th level ATC, chemical substance)
C09BA13	moexipril and diuretics
C09BA15	zofenopril and diuretics
C09BB02	enalapril and lercanidipine
C09BB03	lisinopril and amlodipine
C09BB04	perindopril and amlodipine
C09BB05	ramipril and felodipine
C09BB06	enalapril and nitrendipine
C09BB07	ramipril and amlodipine
C09BB10	trandolapril and verapamil
C09BB12	delapril and manidipine
C09BX01	perindopril, amlodipine and indapamide
C09BX02	perindopril and bisoprolol
C09BX03	ramipril, amlodipine and hydrochlorothiazide
C09BX04	perindopril, bisoprolol and amlodipine
C09CA04	Irbesartan
C09CA07	Telmisartan
C09CA09	Azilsartan
C09DA04	Irbesartan
C09DA07	Hydrochlorothiazide, telmisartan
C09DB01	Valsartan, amlodipine
C09DB04	Amlodipine, telmisartan
C09DX01	Valsartan, hydrochlorothiazide, amlodipine besilate
C09DX04	Sacubitril, valsartan
C09DX07	Hydrochlorothiazide, irbesartan
C09XA02	Aliskiren
C09XA52	Hydrochlorothiazide, aliskiren
C10AA01	simvastatin
C10AA02	lovastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA06	cerivastatin

ATC code	Name (5th level ATC, chemical substance)
C10AA07	rosuvastatin
C10AA08	pitavastatin
C10AB01	clofibrate
C10AB02	bezafibrate
C10AB03	aluminium clofibrate
C10AB04	gemfibrozil
C10AB05	fenofibrate
C10AB06	simfibrate
C10AB07	ronifibrate
C10AB08	ciprofibrate
C10AB09	etofibrate
C10AB10	clofibride
C10AB11	choline fenofibrate
C10AC01	colestyramine
C10AC02	colestipol
C10AC03	colextran
C10AC04	Colesevelam
C10AD01	niceritrol
C10AD02	nicotinic acid
C10AD03	nicofuranose
C10AD04	aluminium nicotinate
C10AD05	nicotinyl alcohol (pyridylcarbinol)
C10AD06	acipimox
C10AD52	nicotinic acid, combinations
C10AX01	dextrothyroxine
C10AX02	probucol
C10AX03	tiadenol
C10AX05	meglutol
C10AX06	omega-3-triglycerides incl. other esters and acids
C10AX07	magnesium pyridoxal 5-phosphate glutamate
C10AX08	policosanol
C10AX09	ezetimibe

ATC code	Name (5th level ATC, chemical substance)
C10AX10	Alipogene tiparvovec
C10AX11	mipomersen
C10AX12	Lomitapide
C10AX13	evolocumab
C10AX14	alirocumab
C10AX15	bempedoic acid
C10BA01	lovastatin and nicotinic acid
C10BA02	simvastatin and ezetimibe
C10BA03	pravastatin and fenofibrate
C10BA04	simvastatin and fenofibrate
C10BA05	atorvastatin and ezetimibe
C10BA06	rosuvastatin and ezetimibe
C10BA07	rosuvastatin and omega-3 fatty acids
C10BA08	atorvastatin and omega-3 fatty acids
C10BA09	rosuvastatin and fenofibrate
C10BX01	simvastatin and acetylsalicylic acid
C10BX02	pravastatin and acetylsalicylic acid
C10BX03	atorvastatin and amlodipine
C10BX04	simvastatin, acetylsalicylic acid and ramipril
C10BX05	rosuvastatin and acetylsalicylic acid
C10BX06	atorvastatin, acetylsalicylic acid and ramipril
C10BX07	rosuvastatin, amlodipine and lisinopril
C10BX08	atorvastatin and acetylsalicylic acid
C10BX09	rosuvastatin and amlodipine
C10BX10	rosuvastatin and valsartan
C10BX11	atorvastatin, amlodipine and perindopril
C10BX12	atorvastatin, acetylsalicylic acid and perindopril
C10BX13	rosuvastatin, perindopril and indapamide
C10BX14	rosuvastatin, amlodipine and perindopril
C10BX15	atorvastatin and perindopril
C10BX16	rosuvastatin and fimasartan
C10BX17	rosuvastatin and ramipril

ATC code	Name (5th level ATC, chemical substance)
D01BA01	griseofulvin
D01BA02	terbinafine
D02BB02	Afamelanotide
D06BB10	Imiquimod
D06BX02	Ingenol mebutate
D11AH01	Tacrolimus
D11AX21	Brimonidine tartrate
G02CX01	Atosiban
G03AA01	etynodiol and ethinylestradiol
G03AA02	quingestanol and ethinylestradiol
G03AA03	lynestrenol and ethinylestradiol
G03AA04	megestrol and ethinylestradiol
G03AA05	norethisterone and ethinylestradiol
G03AA06	norgestrel and ethinylestradiol
G03AA07	levonorgestrel and ethinylestradiol
G03AA08	medroxyprogesterone and ethinylestradiol
G03AA09	desogestrel and ethinylestradiol
G03AA10	gestodene and ethinylestradiol
G03AA11	norgestimate and ethinylestradiol
G03AA12	drospirenone and ethinylestradiol
G03AA13	norelgestromin and ethinylestradiol
G03AA14	nomegestrol and estradiol
G03AA15	chlormadinone and ethinylestradiol
G03AA16	dienogest and ethinylestradiol
G03AA17	medroxyprogesterone and estradiol
G03AB01	megestrol and ethinylestradiol
G03AB02	lynestrenol and ethinylestradiol
G03AB03	levonorgestrel and ethinylestradiol
G03AB04	norethisterone and ethinylestradiol
G03AB05	desogestrel and ethinylestradiol
G03AB06	gestodene and ethinylestradiol
G03AB07	chlormadinone and ethinylestradiol

ATC code	Name (5th level ATC, chemical substance)
G03AB08	dienogest and estradiol
G03AB09	norgestimate and ethinylestradiol
G03AC01	norethisterone
G03AC02	lynestrenol
G03AC03	levonorgestrel
G03AC04	quingestanol
G03AC05	megestrol
G03AC06	medroxyprogesterone
G03AC07	norgestrienone
G03AC08	etonogestrel
G03AC09	desogestrel
G03AC10	drospirenone
G03AD01	levonorgestrel
G03AD02	ulipristal
G03BA01	fluoxymesterone
G03BA02	methyltestosterone
G03BA03	testosterone
G03BB01	mesterolone
G03BB02	androstanolone
G03CA01	ethinylestradiol
G03CA03	estradiol
G03CA04	estriol
G03CA06	chlorotrianisene
G03CA07	estrone
G03CA09	promestriene
G03CA53	estradiol, combinations
G03CA57	conjugated estrogens
G03CB01	dienestrol
G03CB02	diethylstilbestrol
G03CB03	methallenestril
G03CB04	moxestrol
G03CC02	dienestrol

ATC code	Name (5th level ATC, chemical substance)
G03CC03	methallenestril
G03CC04	estrone
G03CC05	diethylstilbestrol
G03CC06	estriol
G03CC07	conjugated estrogens and bazedoxifene
G03CX01	tibolone
G03DA01	gestonorone
G03DA02	medroxyprogesterone
G03DA03	hydroxyprogesterone
G03DA04	progesterone
G03DB01	dydrogesterone
G03DB02	megestrol
G03DB03	medrogestone
G03DB04	nomegestrol
G03DB05	demegestone
G03DB06	chlormadinone
G03DB07	promegestone
G03DB08	dienogest
G03DC01	allylestrenol
G03DC02	norethisterone
G03DC03	lynestrenol
G03DC04	ethisterone
G03DC06	etynodiol
G03DC31	methylestrenolone
G03EA01	methyltestosterone and estrogen
G03EA02	testosterone and estrogen
G03EA03	prasterone and estrogen
G03EK01	methyltestosterone
G03FA01	norethisterone and estrogen
G03FA02	hydroxyprogesterone and estrogen
G03FA03	ethisterone and estrogen
G03FA04	progesterone and estrogen

ATC code	Name (5th level ATC, chemical substance)
G03FA05	methylnortestosterone and estrogen
G03FA06	etynodiol and estrogen
G03FA07	lynestrenol and estrogen
G03FA08	megestrol and estrogen
G03FA09	noretynodrel and estrogen
G03FA10	norgestrel and estrogen
G03FA11	levonorgestrel and estrogen
G03FA12	medroxyprogesterone and estrogen
G03FA13	norgestimate and estrogen
G03FA14	dydrogesterone and estrogen
G03FA15	dienogest and estrogen
G03FA16	trimegestone and estrogen
G03FA17	drospirenone and estrogen
G03FB01	norgestrel and estrogen
G03FB02	lynestrenol and estrogen
G03FB03	chlormadinone and estrogen
G03FB04	megestrol and estrogen
G03FB05	norethisterone and estrogen
G03FB06	medroxyprogesterone and estrogen
G03FB07	medrogestone and estrogen
G03FB08	dydrogesterone and estrogen
G03FB09	levonorgestrel and estrogen
G03FB10	desogestrel and estrogen
G03FB11	trimegestone and estrogen
G03FB12	nomegestrol and estrogen
G03GA05	Follitropin alfa
G03GA06	Follitropin beta
G03GA07	Lutropin alfa
G03GA08	Choriogonadotropin alfa
G03GA09	Corifollitropin alfa
G03GA10	Follitropin delta
G03GA30	Follitropin alfa, lutropin alfa

ATC code	Name (5th level ATC, chemical substance)
G03XB02	Ulipristal
G03XC01	Raloxifene
G03XC02	Bazedoxifene
G04BD04	Oxybutynin
G04BD10	Darifenacin
G04BD11	Fesoterodine
G04BD12	Mirabegron
G04BE03	Sildenafil
G04BE08	Tadalafil
G04BE09	Vardenafil
G04BE10	Avanafil
G04BX15	Pentosan polysulfate
G04CA04	Silodosin
H01AB01	Thyrotropin alfa
H01AC01	Somatropin
H01AC03	Mecasermin
H01AX01	Pegvisomant
H01CB05	Pasireotide
H01CC01	Ganirelix
H01CC02	Cetrorelix
H02AA01	aldosterone
H02AA02	fludrocortisone
H02AA03	desoxycortone
H02AB01	betamethasone
H02AB02	dexamethasone
H02AB03	fluocortolone
H02AB04	methylprednisolone
H02AB05	paramethasone
H02AB06	prednisolone
H02AB07	prednisone
H02AB08	triamcinolone
H02AB09	hydrocortisone

ATC code	Name (5th level ATC, chemical substance)
H02AB10	cortisone
H02AB11	prednylidene
H02AB12	rimexolone
H02AB13	deflazacort
H02AB14	cloprednol
H02AB15	meprednisone
H02AB17	cortivazol
H02BX01	methylprednisolone, combinations
H05AA02	Teriparatide
H05AA03	Parathyroid hormone
H05BX01	Cinacalcet
H05BX04	Etelcalcetide
J01AA01	demeclocycline
J01AA02	doxycycline
J01AA03	chlortetracycline
J01AA04	lymecycline
J01AA05	metacycline
J01AA06	oxytetracycline
J01AA07	tetracycline
J01AA08	minocycline
J01AA09	rolitetracycline
J01AA10	penimepicycline
J01AA11	clomocycline
J01AA12	tigecycline
J01AA13	eravacycline
J01AA14	sarecycline
J01AA15	omadacycline
J01AA20	combinations of tetracyclines
J01AA56	oxytetracycline, combinations
J01BA01	chloramphenicol
J01BA02	thiamphenicol
J01BA52	thiamphenicol, combinations

ATC code	Name (5th level ATC, chemical substance)
J01CA01	ampicillin
J01CA02	pivampicillin
J01CA03	carbenicillin
J01CA04	amoxicillin
J01CA05	carindacillin
J01CA06	bacampicillin
J01CA07	epicillin
J01CA08	pivmecillinam
J01CA09	azlocillin
J01CA10	mezlocillin
J01CA11	mecillinam
J01CA12	piperacillin
J01CA13	ticarcillin
J01CA14	metampicillin
J01CA15	talampicillin
J01CA16	sulbenicillin
J01CA17	temocillin
J01CA18	hetacillin
J01CA19	aspoxicillin
J01CA20	combinations
J01CA51	ampicillin, combinations
J01CE01	benzylpenicillin
J01CE02	phenoxymethylpenicillin
J01CE03	propicillin
J01CE04	azidocillin
J01CE05	pheneticillin
J01CE06	penamecillin
J01CE07	clometocillin
J01CE08	benzathine benzylpenicillin
J01CE09	procaine benzylpenicillin
J01CE10	benzathine phenoxymethylpenicillin
J01CE30	combinations

ATC code	Name (5th level ATC, chemical substance)
J01CF01	dicloxacillin
J01CF02	cloxacillin
J01CF03	meticillin
J01CF04	oxacillin
J01CF05	flucloxacillin
J01CF06	nafcillin
J01CG01	sulbactam
J01CG02	tazobactam
J01CR01	ampicillin and beta-lactamase inhibitor
J01CR02	amoxicillin and beta-lactamase inhibitor
J01CR03	ticarcillin and beta-lactamase inhibitor
J01CR04	sultamicillin
J01CR05	piperacillin and beta-lactamase inhibitor
J01CR50	combinations of penicillins
J01DB01	cefalexin
J01DB02	cefaloridine
J01DB03	cefalotin
J01DB04	cefazolin
J01DB05	cefadroxil
J01DB06	cefazedone
J01DB07	cefatrizine
J01DB08	cefapirin
J01DB09	cefradine
J01DB10	cefacetrile
J01DB11	cefroxadine
J01DB12	ceftezole
J01DC01	cefoxitin
J01DC02	cefuroxime
J01DC03	cefamandole
J01DC04	cefaclor
J01DC05	cefotetan
J01DC06	cefonicid

ATC code	Name (5th level ATC, chemical substance)
J01DC07	cefotiam
J01DC08	loracarbef
J01DC09	cefmetazole
J01DC10	cefprozil
J01DC11	ceforanide
J01DC12	cefminox
J01DC13	cefbuperazone
J01DC14	flomoxef
J01DD01	cefotaxime
J01DD02	ceftazidime
J01DD03	cefsulodin
J01DD04	ceftriaxone
J01DD05	cefmenoxime
J01DD06	latamoxef
J01DD07	ceftizoxime
J01DD08	cefixime
J01DD09	cefodizime
J01DD10	cefetamet
J01DD11	cefpiramide
J01DD12	cefoperazone
J01DD13	cefpodoxime
J01DD14	ceftibuten
J01DD15	cefdinir
J01DD16	cefditoren
J01DD17	cefcapene
J01DD18	cefteram
J01DD51	cefotaxime and beta-lactamase inhibitor
J01DD52	ceftazidime and beta-lactamase inhibitor
J01DD54	ceftriaxone, combinations
J01DD62	cefoperazone and beta-lactamase inhibitor
J01DD63	ceftriaxone and beta-lactamase inhibitor
J01DD64	cefpodoxime and beta-lactamase inhibitor

ATC code	Name (5th level ATC, chemical substance)
J01DE01	cefepime
J01DE02	cefpirome
J01DE03	cefozopran
J01DF01	aztreonam
J01DF02	carumonam
J01DH02	meropenem
J01DH03	ertapenem
J01DH04	doripenem
J01DH05	biapenem
J01DH06	tebipenem pivoxil
J01DH51	imipenem and cilastatin
J01DH52	meropenem and vaborbactam
J01DH55	panipenem and betamipron
J01DI01	ceftobiprole medocaril
J01DI02	ceftaroline fosamil
J01DI03	faropenem
J01DI54	ceftolozane and beta-lactamase inhibitor
J01EA01	trimethoprim
J01EA02	brodimoprim
J01EA03	iclaprim
J01EB01	sulfaisodimidine
J01EB02	sulfamethizole
J01EB03	sulfadimidine
J01EB04	sulfapyridine
J01EB05	sulfafurazole
J01EB06	sulfanilamide
J01EB07	sulfathiazole
J01EB08	sulfathiourea
J01EB20	combinations
J01EC01	sulfamethoxazole
J01EC02	sulfadiazine
J01EC03	sulfamoxole

ATC code	Name (5th level ATC, chemical substance)
J01EC20	combinations
J01ED01	sulfadimethoxine
J01ED02	sulfalene
J01ED03	sulfametomidine
J01ED04	sulfametoxydiazine
J01ED05	sulfamethoxypyridazine
J01ED06	sulfaperin
J01ED07	sulfamerazine
J01ED08	sulfaphenazole
J01ED09	sulfamazone
J01ED20	combinations
J01EE01	sulfamethoxazole and trimethoprim
J01EE02	sulfadiazine and trimethoprim
J01EE03	sulfametrole and trimethoprim
J01EE04	sulfamoxole and trimethoprim
J01EE05	sulfadimidine and trimethoprim
J01EE06	sulfadiazine and tetroxoprim
J01EE07	sulfamerazine and trimethoprim
J01FA15	Telithromycin
J01GA01	streptomycin
J01GA02	streptoduocin
J01GB01	tobramycin
J01GB03	gentamicin
J01GB04	kanamycin
J01GB05	neomycin
J01GB06	amikacin
J01GB07	netilmicin
J01GB08	sisomicin
J01GB09	dibekacin
J01GB10	ribostamycin
J01GB11	isepamicin
J01GB12	arbekacin

ATC code	Name (5th level ATC, chemical substance)
J01GB13	bekanamycin
J01GB14	plazomicin
J01MA01	ofloxacin
J01MA02	ciprofloxacin
J01MA03	pefloxacin
J01MA04	enoxacin
J01MA05	temafloxacin
J01MA06	norfloxacin
J01MA07	lomefloxacin
J01MA08	fleroxacin
J01MA09	sparfloxacin
J01MA10	rufloxacin
J01MA11	grepafloxacin
J01MA12	levofloxacin
J01MA13	trovafloxacin
J01MA14	moxifloxacin
J01MA15	gemifloxacin
J01MA16	gatifloxacin
J01MA17	prulifloxacin
J01MA18	pazufloxacin
J01MA19	garenoxacin
J01MA21	sitafloxacin
J01MA22	tosufloxacin
J01MA23	delafloxacin
J01MB01	rosoxacin
J01MB02	nalidixic acid
J01MB03	piromidic acid
J01MB04	pipemidic acid
J01MB05	oxolinic acid
J01MB06	cinoxacin
J01MB07	flumequine
J01MB08	nemonoxacin

ATC code	Name (5th level ATC, chemical substance)
J01RA03	Cefuroxime and metronidazole
J01RA04	Spiramycin and metronidazole
J01RA10	Ciprofloxacin and metronidazole
J01XA03	Telavancin
J01XA04	Dalbavancin
J01XA05	Oritavancin
J01XB01	Colistimethate
J01XD01	Metronidazole
J01XX09	Daptomycin
J01XX11	Tedizolid phosphate
J02AB02	Ketoconazole
J02AC03	Voriconazole
J02AC04	Posaconazole
J02AC05	Isavuconazole
J02AX04	Caspofungin
J02AX05	Micafungin
J02AX06	Anidulafungin
J04AA01	4-aminosalicylic acid
J04AA02	sodium aminosalicylate
J04AA03	calcium aminosalicylate
J05AA01	metisazone
J05AB01	aciclovir
J05AB02	idoxuridine
J05AB03	vidarabine
J05AB06	ganciclovir
J05AB09	famciclovir
J05AB11	valaciclovir
J05AB12	cidofovir
J05AB13	penciclovir
J05AB14	valganciclovir
J05AB15	brivudine
J05AC02	rimantadine

ATC code	Name (5th level ATC, chemical substance)
J05AC03	tromantadine
J05AE01	saquinavir
J05AE02	indinavir
J05AE03	ritonavir
J05AE04	nelfinavir
J05AE05	amprenavir
J05AE07	fosamprenavir
J05AE08	atazanavir
J05AE09	tipranavir
J05AE10	darunavir
J05AF01	zidovudine
J05AF02	didanosine
J05AF03	zalcitabine
J05AF04	stavudine
J05AF05	lamivudine
J05AF06	abacavir
J05AF07	tenofovir disoproxil
J05AF08	adefovir dipivoxil
J05AF09	emtricitabine
J05AF10	entecavir
J05AF11	telbivudine
J05AF12	clevudine
J05AF13	tenofovir alafenamide
J05AG01	nevirapine
J05AG02	delavirdine
J05AG03	efavirenz
J05AG04	etravirine
J05AG05	rilpivirine
J05AG06	doravirine
J05AH01	zanamivir
J05AH02	oseltamivir
J05AH03	peramivir

ATC code	Name (5th level ATC, chemical substance)
J05AH04	laninamivir
J05AP01	ribavirin
J05AP02	telaprevir
J05AP03	boceprevir
J05AP04	faldaprevir
J05AP05	simeprevir
J05AP06	asunaprevir
J05AP07	daclatasvir
J05AP08	sofosbuvir
J05AP09	dasabuvir
J05AP10	elbasvir
J05AP11	grazoprevir
J05AP51	sofosbuvir and ledipasvir
J05AP52	dasabuvir, ombitasvir, paritaprevir and ritonavir
J05AP53	ombitasvir, paritaprevir and ritonavir
J05AP54	elbasvir and grazoprevir
J05AP55	sofosbuvir and velpatasvir
J05AP56	sofosbuvir, velpatasvir and voxilaprevir
J05AP57	glecaprevir and pibrentasvir
J05AP58	daclatasvir, asunaprevir and beclabuvir
J05AR01	zidovudine and lamivudine
J05AR02	lamivudine and abacavir
J05AR03	tenofovir disoproxil and emtricitabine
J05AR04	zidovudine, lamivudine and abacavir
J05AR05	zidovudine, lamivudine and nevirapine
J05AR06	emtricitabine, tenofovir disoproxil and efavirenz
J05AR07	stavudine, lamivudine and nevirapine
J05AR08	emtricitabine, tenofovir disoproxil and rilpivirine
J05AR09	emtricitabine, tenofovir disoproxil, elvitegravir and cobicistat
J05AR10	lopinavir and ritonavir
J05AR11	lamivudine, tenofovir disoproxil and efavirenz
J05AR12	lamivudine and tenofovir disoproxil

ATC code	Name (5th level ATC, chemical substance)
J05AR13	lamivudine, abacavir and dolutegravir
J05AR14	darunavir and cobicistat
J05AR15	atazanavir and cobicistat
J05AR16	lamivudine and raltegravir
J05AR17	emtricitabine and tenofovir alafenamide
J05AR18	emtricitabine, tenofovir alafenamide, elvitegravir and cobicistat
J05AR19	emtricitabine, tenofovir alafenamide and rilpivirine
J05AR20	emtricitabine, tenofovir alafenamide and bictegravir
J05AR21	dolutegravir and rilpivirine
J05AR22	emtricitabine, tenofovir alafenamide, darunavir and cobicistat
J05AR23	atazanavir and ritonavir
J05AR24	lamivudine, tenofovir disoproxil and doravirine
J05AR25	lamivudine and dolutegravir
J05AR26	darunavir and ritonavir
J05AR27	lamivudine, tenofovir disoproxil and dolutegravir
J05AX01	moroxydine
J05AX02	lysozyme
J05AX05	inosine pranobex
J05AX06	pleconaril
J05AX07	enfuvirtide
J05AX08	raltegravir
J05AX09	maraviroc
J05AX10	maribavir
J05AX11	elvitegravir
J05AX12	dolutegravir
J05AX13	umifenovir
J05AX17	enisamium iodide
J05AX18	letermovir
J05AX19	tilorone
J05AX21	pentanedioic acid imidazolyl ethanamide
J05AX23	ibalizumab
J05AX24	tecovirimat

ATC code	Name (5th level ATC, chemical substance)
J05AX25	baloxavir marboxil
J05AX26	amenamevir
J05AX27	favipiravir
J06BA01	Human normal immunoglobulin
J06BA02	Human normal immunoglobulin
J06BB04	Human hepatitis b immunoglobulin
J06BB16	Palivizumab
J06BB21	Bezlotoxumab
J07AE01	Cholera vaccine (inactivated, oral)
J07AH08	Meningococcal group a, c, w135 and y conjugate vaccine
J07AH09	Meningococcal group b vaccine
J07AL02	Pneumococcus, purified polysaccharides antigen conjugated
J07AL52	Pneumococcus purified polysaccharides antigen and haemophilus influenzae, conjugated
J07BA02	Japanese encephalitis virus (inactivated)
J07BB01	Influenza, inactivated, whole virus
J07BB02	Influenza, inactivated, split virus or surface antigen
J07BB03	Influenza, live attenuated
J07BC01	Hepatitis b vaccine (rdna)
J07BC20	Hepatitis a (inactivated) and hepatitis b (rdna) vaccine (adsorbed)
J07BD52	Measles, mumps and rubella vaccine (live)
J07BD54	Measles, mumps, rubella and varicella vaccine (live)
J07BH02	Rotavirus vaccine, live, oral, pentavalent
J07BK02	Varicella vaccine (live)
J07BM01	papillomavirus (human types 6, 11, 16, 18)
J07BM02	papillomavirus (human types 16, 18)
J07BM03	papillomavirus (human types 6, 11, 16, 18, 31, 33, 45, 52, 58)
J07BX01	smallpox, live attenuated
J07CA05	Diphtheria, tetanus, pertussis and hepatitis b (rdna) vaccine (adsorbed)
J07CA09	Diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rdna), poliomyelitis (inact.) And haemophilus type b conjugate vaccine (adsorbed)
L01AB01	Busulfan

ATC code	Name (5th level ATC, chemical substance)
L01AC01	Thiotepa
L01AX03	Temozolomide
L01BA01	methotrexate
L01BA03	raltitrexed
L01BA04	pemetrexed
L01BA05	pralatrexate
L01BB02	mercaptopurine
L01BB03	tioguanine
L01BB04	cladribine
L01BB05	fludarabine
L01BB06	clofarabine
L01BB07	nelarabine
L01BC01	cytarabine
L01BC02	fluorouracil
L01BC03	tegafur
L01BC04	carmofur
L01BC05	gemcitabine
L01BC06	capecitabine
L01BC07	azacitidine
L01BC08	decitabine
L01BC09	floxuridine
L01BC52	fluorouracil, combinations
L01BC53	tegafur, combinations
L01BC59	trifluridine, combinations
L01CA05	Vinflunine
L01CD01	Paclitaxel
L01CD02	Docetaxel
L01CD04	Cabazitaxel
L01CX01	Trabectedin
L01DB01	Doxorubicin
L01DB11	Pixantrone
L01XC02	Rituximab

ATC code	Name (5th level ATC, chemical substance)
L01XC03	Trastuzumab
L01XC06	Cetuximab
L01XC07	Bevacizumab
L01XC08	Panitumumab
L01XC11	Ipilimumab
L01XC12	Brentuximab vedotin
L01XC13	Pertuzumab
L01XC14	Trastuzumab emtansine
L01XC15	Obinutuzumab
L01XC16	Dinutuximab
L01XC17	Nivolumab
L01XC18	Pembrolizumab
L01XC19	Blinatumomab
L01XC21	Ramucirumab
L01XC22	Necitumumab
L01XC23	Elotuzumab
L01XC24	Daratumumab
L01XC26	Inotuzumab ozogamicin
L01XC27	Olaratumab
L01XD04	Aminolevulinic acid
L01XD05	Temoporfin
L01XE01	Imatinib
L01XE03	Erlotinib
L01XE04	Sunitinib
L01XE05	Sorafenib
L01XE06	Dasatinib
L01XE07	Lapatinib
L01XE08	Nilotinib
L01XE09	Temsirolimus
L01XE10	Everolimus
L01XE11	Pazopanib
L01XE12	Vandetanib

ATC code	Name (5th level ATC, chemical substance)
L01XE13	Afatinib
L01XE14	Bosutinib
L01XE15	Vemurafenib
L01XE16	Crizotinib
L01XE17	Axitinib
L01XE18	Ruxolitinib
L01XE21	Regorafenib
L01XE23	Dabrafenib
L01XE24	Ponatinib
L01XE25	Trametinib
L01XE26	Cabozantinib
L01XE27	Ibrutinib
L01XE29	Lenvatinib
L01XE31	Nintedanib
L01XE33	Palbociclib
L01XE38	Cobimetinib
L01XX02	Asparaginase
L01XX05	Hydroxycarbamide
L01XX19	Irinotecan
L01XX22	Alitretinoin
L01XX23	Mitotane
L01XX24	Pegaspargase
L01XX25	Bexarotene
L01XX27	Arsenic
L01XX32	Bortezomib
L01XX35	Anagrelide
L01XX41	Eribulin
L01XX42	Panobinostat
L01XX43	Vismodegib
L01XX44	Aflibercept
L01XX45	Carfilzomib
L01XX46	Olaparib

ATC code	Name (5th level ATC, chemical substance)
L01XX48	Sonidegib
L01XX50	Ixazomib
L01XX51	Talimogene laherparepvec
L02BA02	Toremifene
L02BA03	Fulvestrant
L02BB04	Enzalutamide
L02BX02	Degarelix
L03AA02	filgrastim
L03AA03	molgramostim
L03AA09	sargramostim
L03AA10	lenograstim
L03AA12	ancestim
L03AA13	pegfilgrastim
L03AA14	lipegfilgrastim
L03AA15	balugrastim
L03AA16	empegfilgrastim
L03AA17	pegteograstim
L03AB01	interferon alfa natural
L03AB02	interferon beta natural
L03AB03	interferon gamma
L03AB04	interferon alfa-2a
L03AB05	interferon alfa-2b
L03AB06	interferon alfa-n1
L03AB07	interferon beta-1a
L03AB08	interferon beta-1b
L03AB09	interferon alfacon-1
L03AB10	peginterferon alfa-2b
L03AB11	peginterferon alfa-2a
L03AB12	albinterferon alfa-2b
L03AB13	peginterferon beta-1a
L03AB14	cepeginterferon alfa-2b
L03AB15	ropeginterferon alfa-2b

ATC code	Name (5th level ATC, chemical substance)
L03AB60	peginterferon alfa-2b, combinations
L03AB61	peginterferon alfa-2a, combinations
L03AC01	aldesleukin
L03AC02	oprelvekin
L03AX01	lentinan
L03AX02	roquinimex
L03AX03	BCG vaccine
L03AX04	pegademase
L03AX05	pidotimod
L03AX07	poly I:C
L03AX08	poly ICLC
L03AX09	thymopentin
L03AX10	immunocyanin
L03AX11	tasonermin
L03AX12	melanoma vaccine
L03AX13	glatiramer acetate
L03AX14	histamine dihydrochloride
L03AX15	mifamurtide
L03AX16	plerixafor
L03AX17	sipuleucel-T
L03AX18	cridanimod
L03AX19	dasiprotimut-T
L03AX21	elapegademase
L04AA02	muromonab-CD3
L04AA03	antilymphocyte immunoglobulin (horse)
L04AA04	antithymocyte immunoglobulin (rabbit)
L04AA06	mycophenolic acid
L04AA10	sirolimus
L04AA13	leflunomide
L04AA15	alefacept
L04AA18	everolimus
L04AA19	gusperimus

ATC code	Name (5th level ATC, chemical substance)
L04AA21	efalizumab
L04AA22	abetimus
L04AA23	natalizumab
L04AA24	abatacept
L04AA25	eculizumab
L04AA26	belimumab
L04AA27	fingolimod
L04AA28	belatacept
L04AA29	tofacitinib
L04AA31	teriflunomide
L04AA32	apremilast
L04AA33	vedolizumab
L04AA34	alemtuzumab
L04AA35	begelomab
L04AA36	ocrelizumab
L04AA37	baricitinib
L04AA38	ozanimod
L04AA39	emapalumab
L04AA40	cladribine
L04AA41	imlifidase
L04AA42	siponimod
L04AA43	ravulizumab
L04AA44	upadacitinib
L04AB01	etanercept
L04AB02	infliximab
L04AB03	afelimomab
L04AB04	adalimumab
L04AB05	certolizumab pegol
L04AB06	golimumab
L04AB07	opinercept
L04AC01	daclizumab
L04AC02	basiliximab

ATC code	Name (5th level ATC, chemical substance)
L04AC03	anakinra
L04AC04	rilonacept
L04AC05	ustekinumab
L04AC07	tocilizumab
L04AC08	canakinumab
L04AC09	briakinumab
L04AC10	secukinumab
L04AC11	siltuximab
L04AC12	brodalumab
L04AC13	ixekizumab
L04AC14	sarilumab
L04AC15	sirukumab
L04AC16	guselkumab
L04AC17	tildrakizumab
L04AC18	risankizumab
L04AD01	ciclosporin
L04AD02	tacrolimus
L04AD03	voclosporin
L04AX01	azathioprine
L04AX02	thalidomide
L04AX03	methotrexate
L04AX04	lenalidomide
L04AX05	pirfenidone
L04AX06	pomalidomide
L04AX07	dimethyl fumarate
L04AX08	darvadstrocel
M01AA01	phenylbutazone
M01AA02	mofebutazone
M01AA03	oxyphenbutazone
M01AA05	clofezone
M01AA06	kebuzone
M01AB01	indometacin

ATC code	Name (5th level ATC, chemical substance)
M01AB02	sulindac
M01AB03	tolmetin
M01AB04	zomepirac
M01AB05	diclofenac
M01AB06	alclofenac
M01AB07	bumadizone
M01AB08	etodolac
M01AB09	lonazolac
M01AB10	fentiazac
M01AB11	acemetacin
M01AB12	difenpiramide
M01AB13	oxametacin
M01AB14	proglumetacin
M01AB15	ketorolac
M01AB16	aceclofenac
M01AB17	bufexamac
M01AB51	indometacin, combinations
M01AB55	diclofenac, combinations
M01AC01	piroxicam
M01AC02	tenoxicam
M01AC04	droxicam
M01AC05	lornoxicam
M01AC06	meloxicam
M01AC56	meloxicam, combinations
M01AE01	ibuprofen
M01AE02	naproxen
M01AE03	ketoprofen
M01AE04	fenoprofen
M01AE05	fenbufen
M01AE06	benoxaprofen
M01AE07	suprofen
M01AE08	pirprofen

ATC code	Name (5th level ATC, chemical substance)
M01AE09	flurbiprofen
M01AE10	indoprofen
M01AE11	tiaprofenic acid
M01AE12	oxaprozin
M01AE13	ibuproxam
M01AE14	dexibuprofen
M01AE15	flunoxaprofen
M01AE16	alminoprofen
M01AE17	dexketoprofen
M01AE18	naproxcinod
M01AE51	ibuprofen, combinations
M01AE52	naproxen and esomeprazole
M01AE53	ketoprofen, combinations
M01AE56	naproxen and misoprostol
M01AG01	mefenamic acid
M01AG02	tolfenamic acid
M01AG03	flufenamic acid
M01AG04	meclofenamic acid
M01AH01	celecoxib
M01AH02	rofecoxib
M01AH03	valdecoxib
M01AH04	parecoxib
M01AH05	etoricoxib
M01AH06	lumiracoxib
M01AH07	polmacoxib
M01AX01	nabumetone
M01AX02	niflumic acid
M01AX04	azapropazone
M01AX05	glucosamine
M01AX07	benzydamine
M01AX12	glucosaminoglycan polysulfate
M01AX13	proquazone

ATC code	Name (5th level ATC, chemical substance)
M01AX14	orgotein
M01AX17	nimesulide
M01AX18	feprazone
M01AX21	diacerein
M01AX22	morniflumate
M01AX23	tenidap
M01AX24	oxaceprol
M01AX25	chondroitin sulfate
M01AX26	avocado and soyabean oil, unsaponifiables
M01AX68	feprazone, combinations
M03AX01	Botulinum b toxin
M03BA01	phenprobamate
M03BA02	carisoprodol
M03BA03	methocarbamol
M03BA04	styramate
M03BA05	febarbamate
M03BA51	phenprobamate, combinations excl. psycholeptics
M03BA52	carisoprodol, combinations excl. psycholeptics
M03BA53	methocarbamol, combinations excl. psycholeptics
M03BA71	phenprobamate, combinations with psycholeptics
M03BA72	carisoprodol, combinations with psycholeptics
M03BA73	methocarbamol, combinations with psycholeptics
M03BB02	chlormezanone
M03BB03	chlorzoxazone
M03BB52	chlormezanone, combinations excl. psycholeptics
M03BB53	chlorzoxazone, combinations excl. psycholeptics
M03BB72	chlormezanone, combinations with psycholeptics
M03BB73	chlorzoxazone, combinations with psycholeptics
M03BC01	orphenadrine (citrate)
M03BC51	orphenadrine, combinations
M03BX01	baclofen
M03BX02	tizanidine

ATC code	Name (5th level ATC, chemical substance)
M03BX03	pridinol
M03BX04	tolperisone
M03BX05	thiocolchicoside
M03BX06	mephenesin
M03BX07	tetrazepam
M03BX08	cyclobenzaprine
M03BX09	eperisone
M03BX30	fenyramidol
M03BX55	thiocolchicoside, combinations
M03CA01	dantrolene
M04AA03	Febuxostat
M04AB05	Lesinurad
M05BA06	Ibandronic acid
M05BA08	Zoledronic acid
M05BB03	Alendronic acid, colecalciferol
M05BC01	Dibotermin alfa
M05BX03	Strontium ranelate
M05BX04	Denosumab
M09AB02	Collagenase
M09AX03	Ataluren
M09AX07	Nusinersen
N01AA01	diethyl ether
N01AA02	vinyl ether
N01AB01	halothane
N01AB02	chloroform
N01AB04	enflurane
N01AB05	trichloroethylene
N01AB06	isoflurane
N01AB07	desflurane
N01AB08	sevoflurane
N01AF01	methohexital
N01AF02	hexobarbital

ATC code	Name (5th level ATC, chemical substance)
N01AF03	thiopental
N01AG01	narcobarbital
N01AH01	fentanyl
N01AH02	alfentanil
N01AH03	sufentanil
N01AH04	phenoperidine
N01AH05	anileridine
N01AH06	remifentanil
N01AH51	fentanyl, combinations
N01AX03	ketamine
N01AX04	propanidid
N01AX05	alfaxalone
N01AX07	etomidate
N01AX10	propofol
N01AX11	sodium oxybate
N01AX13	nitrous oxide
N01AX14	esketamine
N01AX15	xenon
N01AX63	nitrous oxide, combinations
N01BB20	Lidocaine, prilocaine
N01BX04	Capsaicin
N02AB03	Fentanyl
N02BG08	Ziconotide
N03AF03	Rufinamide
N03AF04	Eslicarbazepine
N03AX15	Zonisamide
N03AX16	Pregabalin
N03AX17	Stiripentol
N03AX18	Lacosamide
N03AX21	Retigabine
N03AX22	Perampanel
N03AX23	Brivaracetam

ATC code	Name (5th level ATC, chemical substance)
N04AA01	trihexyphenidyl
N04AA02	biperiden
N04AA03	metixene
N04AA04	procyclidine
N04AA05	profenamine
N04AA08	dexetimide
N04AA09	phenglutarimide
N04AA10	mazaticol
N04AA11	bornaprine
N04AA12	tropatepine
N04AB01	etanautine
N04AB02	orphenadrine (chloride)
N04AC01	benzatropine
N04AC30	etybenzatropine
N04BA02	Carbidopa, levodopa
N04BA03	Carbidopa, entacapone, levodopa
N04BC05	Pramipexole
N04BC09	Rotigotine
N04BD02	Rasagiline
N04BD03	Safinamide
N04BX01	Tolcapone
N04BX02	Entacapone
N04BX04	Opicapone
N05AE05	Lurasidone
N05AH01	Loxapine
N05AH03	Olanzapine
N05AH05	Asenapine
N05AX12	Aripiprazole
N05AX13	Paliperidone
N05CA01	pentobarbital
N05CA02	amobarbital
N05CA03	butobarbital

ATC code	Name (5th level ATC, chemical substance)
N05CA04	barbital
N05CA05	aprobarbital
N05CA06	secobarbital
N05CA07	talbutal
N05CA08	vinylbital
N05CA09	vinbarbital
N05CA10	cyclobarbital
N05CA11	heptabarbital
N05CA12	reposal
N05CA15	methohexital
N05CA16	hexobarbital
N05CA19	thiopental
N05CA20	etallobarbital
N05CA21	allobarbital
N05CA22	proxibarbal
N05CB01	combinations of barbiturates
N05CB02	barbiturates in combination with other drugs
N05CC01	chloral hydrate
N05CC02	chloralodol
N05CC03	acetylglycinamide chloral hydrate
N05CC04	dichloralphenazone
N05CC05	paraldehyde
N05CD01	flurazepam
N05CD02	nitrazepam
N05CD03	flunitrazepam
N05CD04	estazolam
N05CD05	triazolam
N05CD06	lormetazepam
N05CD07	temazepam
N05CD08	midazolam
N05CD09	brotizolam
N05CD10	quazepam

ATC code	Name (5th level ATC, chemical substance)
N05CD11	loprazolam
N05CD12	doxefazepam
N05CD13	cinolazepam
N05CD14	remimazolam
N05CE01	glutethimide
N05CE02	methyprylon
N05CE03	pyrithyldione
N05CF01	zopiclone
N05CF02	zolpidem
N05CF03	zaleplon
N05CF04	eszopiclone
N05CH01	melatonin
N05CH02	ramelteon
N05CH03	tasimelteon
N05CM01	methaqualone
N05CM02	clomethiazole
N05CM03	bromisoval
N05CM04	carbromal
N05CM05	scopolamine
N05CM06	propiomazine
N05CM07	triclofos
N05CM08	ethchlorvynol
N05CM09	Valerianae radix
N05CM10	hexapropymate
N05CM11	bromides
N05CM12	apronal
N05CM13	valnoctamide
N05CM15	methylpentynol
N05CM16	niaprazine
N05CM18	dexmedetomidine
N05CM19	suvorexant
N05CX01	meprobamate, combinations

ATC code	Name (5th level ATC, chemical substance)
N05CX02	methaqualone, combinations
N05CX03	methylpentynol, combinations
N05CX04	clomethiazole, combinations
N05CX05	emepronium, combinations
N05CX06	dipiperonylaminoethanol, combinations
N06AA01	desipramine
N06AA02	imipramine
N06AA03	imipramine oxide
N06AA04	clomipramine
N06AA05	opipramol
N06AA06	trimipramine
N06AA07	lofepramine
N06AA08	dibenzepin
N06AA09	amitriptyline
N06AA10	nortriptyline
N06AA11	protriptyline
N06AA12	doxepin
N06AA13	iprindole
N06AA14	melitracen
N06AA15	butriptyline
N06AA16	dosulepin
N06AA17	amoxapine
N06AA18	dimetacrine
N06AA19	amineptine
N06AA21	maprotiline
N06AA23	quinupramine
N06AB02	zimeldine
N06AB03	fluoxetine
N06AB04	citalopram
N06AB05	paroxetine
N06AB06	sertraline
N06AB07	alaproclate

ATC code	Name (5th level ATC, chemical substance)
N06AB08	fluvoxamine
N06AB09	etoperidone
N06AB10	escitalopram
N06AF01	isocarboxazid
N06AF02	nialamide
N06AF03	phenelzine
N06AF04	tranylcypromine
N06AF05	iproniazide
N06AF06	iproclozide
N06AG02	moclobemide
N06AG03	toloxatone
N06AX01	oxitriptan
N06AX02	tryptophan
N06AX03	mianserin
N06AX04	nomifensine
N06AX05	trazodone
N06AX06	nefazodone
N06AX07	minaprine
N06AX08	bifemelane
N06AX09	viloxazine
N06AX10	oxaflozane
N06AX11	mirtazapine
N06AX12	bupropion
N06AX13	medifoxamine
N06AX14	tianeptine
N06AX15	pivagabine
N06AX16	venlafaxine
N06AX17	milnacipran
N06AX18	reboxetine
N06AX19	gepirone
N06AX21	duloxetine
N06AX22	agomelatine

ATC code	Name (5th level ATC, chemical substance)
N06AX23	desvenlafaxine
N06AX24	vilazodone
N06AX25	Hyperici herba
N06AX26	vortioxetine
N06AX27	esketamine
N06BA01	amfetamine
N06BA02	dexamfetamine
N06BA03	metamfetamine
N06BA04	methylphenidate
N06BA05	pemoline
N06BA06	fencamfamin
N06BA07	modafinil
N06BA08	fenozolone
N06BA09	atomoxetine
N06BA10	fenetylline
N06BA11	dexmethylphenidate
N06BA12	lisdexamfetamine
N06BA13	armodafinil
N06BA14	solriamfetol
N06BC01	caffeine
N06BC02	propentofylline
N06BX01	meclofenoxate
N06BX02	pyritinol
N06BX03	piracetam
N06BX04	deanol
N06BX05	fipexide
N06BX06	citicoline
N06BX07	oxiracetam
N06BX08	pirisudanol
N06BX09	linopirdine
N06BX10	nizofenone
N06BX11	aniracetam

ATC code	Name (5th level ATC, chemical substance)
N06BX12	acetylcarnitine
N06BX13	idebenone
N06BX14	prolintane
N06BX15	pipradrol
N06BX16	pramiracetam
N06BX17	adrafinil
N06BX18	vinpocetine
N06BX21	tetramethylglycoluril
N06BX22	phenibut
N06DA03	Rivastigmine
N06DX01	Memantine
N07BA01	nicotine
N07BA03	varenicline
N07BA04	cytisine
N07BB01	disulfiram
N07BB02	calcium carbimide
N07BB03	acamprosate
N07BB04	naltrexone
N07BB05	nalmefene
N07BC01	buprenorphine
N07BC02	methadone
N07BC03	levacetylmethadol
N07BC04	lofexidine
N07BC05	levomethadone
N07BC06	diamorphine
N07BC51	buprenorphine, combinations
N07CA01	betahistine
N07CA02	cinnarizine
N07CA03	flunarizine
N07CA04	acetylleucine
N07CA52	cinnarizine, combinations
N07XX02	Riluzole

ATC code	Name (5th level ATC, chemical substance)
N07XX04	Sodium oxybate
N07XX05	Amifampridine
N07XX07	Fampridine
N07XX11	Pitolisant
P01AB01	metronidazole
P01AB02	tinidazole
P01AB03	ornidazole
P01AB04	azanidazole
P01AB05	propenidazole
P01AB06	nimorazole
P01AB07	secnidazole
P01AB51	metronidazole, combinations
P01BA01	chloroquine
P01BA02	hydroxychloroquine
P01BA03	primaquine
P01BA06	amodiaquine
P01BA07	tafenoquine
P01BB01	proguanil
P01BB02	cycloguanil embonate
P01BB51	proguanil, combinations
P01BC01	quinine
P01BC02	mefloquine
P01BD01	pyrimethamine
P01BD51	pyrimethamine, combinations
P01BE01	artemisinin
P01BE02	artemether
P01BE03	artesunate
P01BE04	artemotil
P01BE05	artenimol
P01BF01	artemether and lumefantrine
P01BF02	artesunate and mefloquine
P01BF03	artesunate and amodiaquine

ATC code	Name (5th level ATC, chemical substance)
P01BF04	artesunate, sulphamethopyrazine and pyrimethamine
P01BF05	artenimol and piperaquine
P01BF06	artesunate and pyronaridine
P01BX01	halofantrine
P01BX02	arterolane and piperaquine
P01CX03	Eflornithine
R01AD12	Fluticasone furoate
R01BA01	phenylpropanolamine
R01BA02	pseudoephedrine
R01BA03	phenylephrine
R01BA51	phenylpropanolamine, combinations
R01BA52	pseudoephedrine, combinations
R01BA53	phenylephrine, combinations
R03AA01	epinephrine
R03AB02	isoprenaline
R03AB03	orciprenaline
R03AC02	salbutamol
R03AC03	terbutaline
R03AC04	fenoterol
R03AC05	rimiterol
R03AC06	hexoprenaline
R03AC07	isoetarine
R03AC08	pirbuterol
R03AC09	tretoquinol
R03AC10	carbuterol
R03AC11	tulobuterol
R03AC12	salmeterol
R03AC13	formoterol
R03AC14	clenbuterol
R03AC15	reproterol
R03AC16	procaterol
R03AC17	bitolterol

ATC code	Name (5th level ATC, chemical substance)
R03AC18	indacaterol
R03AC19	olodaterol
R03AK01	epinephrine and other drugs for obstructive airway diseases
R03AK02	isoprenaline and other drugs for obstructive airway diseases
R03AK04	salbutamol and sodium cromoglicate
R03AK05	reproterol and sodium cromoglicate
R03AK06	salmeterol and fluticasone
R03AK07	formoterol and budesonide
R03AK08	formoterol and beclometasone
R03AK09	formoterol and mometasone
R03AK10	vilanterol and fluticasone furoate
R03AK11	formoterol and fluticasone
R03AK12	salmeterol and budesonide
R03AK13	salbutamol and beclometasone
R03AK14	indacaterol and mometasone
R03AL01	fenoterol and ipratropium bromide
R03AL02	salbutamol and ipratropium bromide
R03AL03	vilanterol and umeclidinium bromide
R03AL04	indacaterol and glycopyrronium bromide
R03AL05	formoterol and aclidinium bromide
R03AL06	olodaterol and tiotropium bromide
R03AL07	formoterol and glycopyrronium bromide
R03AL08	vilanterol, umeclidinium bromide and fluticasone furoate
R03AL09	formoterol, glycopyrronium bromide and beclometasone
R03AL10	formoterol and tiotropium bromide
R03AL11	formoterol, glycopyrronium bromide and budesonide
R03AL12	indacaterol, glycopyrronium bromide and mometasone
R03BB05	Aclidinium
R03BB06	Glycopyrronium
R03BB07	Umeclidinium bromide
R03CA02	ephedrine
R03CB01	isoprenaline

ATC code	Name (5th level ATC, chemical substance)
R03CB02	methoxyphenamine
R03CB03	orciprenaline
R03CB51	isoprenaline, combinations
R03CB53	orciprenaline, combinations
R03CC02	salbutamol
R03CC03	terbutaline
R03CC04	fenoterol
R03CC05	hexoprenaline
R03CC06	isoetarine
R03CC07	pirbuterol
R03CC08	procaterol
R03CC09	tretoquinol
R03CC10	carbuterol
R03CC11	tulobuterol
R03CC12	bambuterol
R03CC13	clenbuterol
R03CC14	reproterol
R03CC53	terbutaline, combinations
R03CC63	clenbuterol and ambroxol
R03DX05	Omalizumab
R03DX07	Roflumilast
R03DX09	Mepolizumab
R05CB16	Mannitol
R06AA01	bromazine
R06AA02	diphenhydramine
R06AA04	clemastine
R06AA06	chlorphenoxamine
R06AA07	diphenylpyraline
R06AA08	carbinoxamine
R06AA09	doxylamine
R06AA10	trimethobenzamide
R06AA52	diphenhydramine, combinations

ATC code	Name (5th level ATC, chemical substance)
R06AA54	clemastine, combinations
R06AA56	chlorphenoxamine, combinations
R06AA57	diphenylpyraline, combinations
R06AA59	doxylamine, combinations
R06AB01	brompheniramine
R06AB02	dexchlorpheniramine
R06AB03	dimetindene
R06AB04	chlorphenamine
R06AB05	pheniramine
R06AB06	dexbrompheniramine
R06AB07	talastine
R06AB51	brompheniramine, combinations
R06AB52	dexchlorpheniramine, combinations
R06AB54	chlorphenamine, combinations
R06AB56	dexbrompheniramine, combinations
R06AC01	mepyramine
R06AC02	histapyrrodine
R06AC03	chloropyramine
R06AC04	tripelennamine
R06AC05	methapyrilene
R06AC06	thonzylamine
R06AC52	histapyrrodine, combinations
R06AC53	chloropyramine, combinations
R06AD01	alimemazine
R06AD02	promethazine
R06AD03	thiethylperazine
R06AD04	methdilazine
R06AD05	hydroxyethylpromethazine
R06AD06	thiazinam
R06AD07	mequitazine
R06AD08	oxomemazine
R06AD09	isothipendyl

ATC code	Name (5th level ATC, chemical substance)
R06AD52	promethazine, combinations
R06AD55	hydroxyethylpromethazine, combinations
R06AE01	buclizine
R06AE03	cyclizine
R06AE04	chlorcyclizine
R06AE05	meclozine
R06AE06	oxatomide
R06AE07	cetirizine
R06AE09	levocetirizine
R06AE51	buclizine, combinations
R06AE53	cyclizine, combinations
R06AE55	meclozine, combinations
R06AX01	bamipine
R06AX02	cyproheptadine
R06AX03	thenalidine
R06AX04	phenindamine
R06AX05	antazoline
R06AX07	triprolidine
R06AX08	pyrrobutamine
R06AX09	azatadine
R06AX11	astemizole
R06AX12	terfenadine
R06AX13	loratadine
R06AX15	mebhydrolin
R06AX16	deptropine
R06AX17	ketotifen
R06AX18	acrivastine
R06AX19	azelastine
R06AX21	tritoqualine
R06AX22	ebastine
R06AX23	pimethixene
R06AX24	epinastine

ATC code	Name (5th level ATC, chemical substance)
R06AX25	mizolastine
R06AX26	fexofenadine
R06AX27	desloratadine
R06AX28	rupatadine
R06AX29	bilastine
R06AX31	quifenadine
R06AX32	sequifenadine
R06AX53	thenalidine, combinations
R06AX58	pyrrobutamine, combinations
R07AX01	Nitric oxide
R07AX02	Ivacaftor
R07AX30	Lumacaftor, ivacaftor
S01BA01	Dexamethasone
S01BC10	Nepafenac
S01EC04	Brinzolamide
S01EC54	Brinzolamide, brimonidine tartrate
S01ED51	Timolol, combinations
S01EE03	Bimatoprost
S01EE04	Travoprost
S01FB51	Ketorolac, phenylephrine
S01GX06	Emedastine
S01GX09	Olopatadine
S01LA01	Verteporfin
S01LA03	Pegaptanib
S01LA04	Ranibizumab
S01LA05	Aflibercept
S01XA19	limbal stem cells, autologous
S01XA22	Ocriplasmin
V03AB17	Methylthioninium
V03AB33	Hydroxocobalamin
V03AB35	Sugammadex
V03AC02	Deferiprone

ATC code	Name (5th level ATC, chemical substance)
V03AC03	Deferasirox
V03AE05	Sucroferric oxyhydroxide
V03AE08	Ferric citrate coordination complex
V03AF02	Dexrazoxane
V03AF07	Rasburicase
V03AX03	Cobicistat
V08CA06	Gadoversetamide
V08DA01	Perflutren, human albumin microspheres
V08DA04	Perflutren, phospholipid microspheres
V08DA05	sulfur hexafluoride, phospholipid microspheres
V09AB03	Ioflupane (123i)
V09AX04	Flutemetamol (18f)
V09AX05	Florbetapir (18f)
V09AX06	Florbetaben (18f)
V09IA09	Tilmanocept
V09IX12	Fluciclovine (18f)
V10BX02	Samarium (153sm) lexidronam
V10XX02	Ibritumomab tiuxetan

ATC: Anatomical Therapeutic Chemical; CD3: Cluster of differentiation 3; poly I:C: polyinosinic-polycytidylic acid.

Table 55: Concomitant medicines to valproate-indicated psychiatric conditions

ATC code	Name (5th level ATC, chemical substance)
Valproate indication: Bipolar disorder	
C09BB10	Verapamil
N03AE01	Clonazepam
N03AF01	Carbamazepine
N04BC05	Pramipexole
N05AA01	Chlorpromazine
N05AA02	Levomepromazine
N05AA03	Promazine
N05AA04	Acepromazine
N05AA05	Trifluprom azine

ATC code	Name (5th level ATC, chemical substance)
N05AA06	Cyamemazine
N05AA07	Chlorproethazine
N05AB01	Dixyrazine
N05AB02	Fluphenazine
N05AB03	Perphenazine
N05AB04	Prochlorperazine
N05AB05	Thiopropazate
N05AB06	Trifluoperazine
N05AB07	Acetophenazine
N05AB08	Thioproperazine
N05AB09	Butaperazine
N05AB10	Perazine
N05AC01	Periciazine
N05AC02	Thioridazine
N05AC03	Mesoridazine
N05AC04	Pipotiazine
N05AD01	Haloperidol
N05AD02	Trifluperidol
N05AD03	Melperone
N05AD04	Moperone
N05AD05	Pipamperone
N05AD06	Bromperidol
N05AD07	Benperidol
N05AD08	Droperidol
N05AD09	Fluanisone
N05AE01	Oxypertine
N05AE02	Molindone
N05AE03	Sertindole
N05AE04	Ziprasidone
N05AE05	Lurasidone
N05AF01	Flupentixol

ATC code	Name (5th level ATC, chemical substance)
N05AF02	Clopenthixol
N05AF03	Chlorprothixene
N05AF04	Tiotixene
N05AF05	Zuclopenthixol
N05AG01	Fluspirilene
N05AG02	Pimozide
N05AG03	Penfluridol
N05AH01	Loxapine
N05AH02	Clozapine
N05AH03	Olanzapine
N05AH04	Quetiapine
N05AH05	Asenapine
N05AH06	Clotiapine
N05AL01	Sulpiride
N05AL02	Sultopride
N05AL03	Tiapride
N05AL04	Remoxipride
N05AL05	Amisulpride
N05AL06	Veralipride
N05AL07	levosulpiride
N05AN01	lithium
N05AX07	Prothipendyl
N05AX08	Risperidone
N05AX10	Mosapramine
N05AX11	Zotepine
N05AX12	Aripiprazole
N05AX13	Paliperidone
N05AX14	Iloperidone
N05AX15	Cariprazine
N05AX16	Brexpiprazole
N05AX17	Pimavanserin

ATC code	Name (5th level ATC, chemical substance)
N06AA01	Desipramine
N06AA02	Imipramine
N06AA03	Imipramine oxide
N06AA04	Clomipramine
N06AA05	Opipramol
N06AA06	Trimipramine
N06AA07	Lofepramine
N06AA08	Dibenzepin
N06AA09	Amitriptyline
N06AA10	Nortriptyline
N06AA11	Protriptyline
N06AA12	Doxepin
N06AA13	Iprindole
N06AA14	Melitracen
N06AA15	Butriptyline
N06AA16	Dosulepin
N06AA17	Amoxapine
N06AA18	Dimetacrine
N06AA19	Amineptine
N06AA21	Maprotiline
N06AA23	Quinupramine
N06AB02	Zimeldine
N06AB03	Fluoxetine
N06AB04	Citalopram
N06AB05	Paroxetine
N06AB06	Sertraline
N06AB07	Alaproclate
N06AB08	Fluvoxamine
N06AB09	Etoperidone
N06AB10	Escitalopram
N06AF01	Isocarboxazid

ATC code	Name (5th level ATC, chemical substance)
N06AF02	Nialamide
N06AF03	Phenelzine
N06AF04	Tranylcypromine
N06AF05	Iproniazide
N06AF06	Iproclozide
N06AG02	Moclobemide
N06AG03	Toloxatone
N06AX01	Oxitriptan
N06AX02	Tryptophan
N06AX03	Mianserin
N06AX04	Nomifensine
N06AX05	Trazodone
N06AX06	Nefazodone
N06AX07	Minaprine
N06AX08	Bifemelane
N06AX09	Viloxazine
N06AX10	Oxaflozane
N06AX11	Mirtazapine
N06AX12	Bupropion
N06AX13	Medifoxamine
N06AX14	Tianeptine
N06AX15	Pivagabine
N06AX16	Venlafaxine
N06AX17	Milnacipran
N06AX18	Reboxetine
N06AX19	Gepirone
N06AX21	Duloxetine
N06AX22	Agomelatine
N06AX23	Desvenlafaxine
N06AX24	Vilazodone
N06AX25	Hyperici herba

ATC code	Name (5th level ATC, chemical substance)
N06AX26	Vortioxetine
N06AX27	Esketamine
N06CA01	Amitriptyline and psycholeptics
N06CA02	Melitrecen and psycholeptics
N06CA03	Fluoxetine and psycholeptics
Valproate indication: Mania	
C09BB10	Verapamil
N03AE01	Clonazepam
N03AF01	Carbamazepine
N05AA01	Chlorpromazine
N05AB08	Thioproperazine
N05AD01	Haloperidol
N05AE04	Ziprasidone
N05AH02	Clozapine
N05AH03	Olanzapine
N05AH04	Quetiapine
N05AH05	Asenapine
N05AL05	Amisulpride
N05AN01	lithium
N05AX08	Risperidone
N05AX11	Zotepine
N05AX12	Aripiprazole
N05AX15	Cariprazine
N05BA01	Diazepam
N05BA02	Chlordiazepoxide
N05BA03	Medazepam
N05BA04	Oxazepam
N05BA05	Potassium clorazepate
N05BA06	Lorazepam
N05BA07	Adinazolam
N05BA08	Bromazepam

ATC code	Name (5th level ATC, chemical substance)
N05BA09	Clobazam
N05BA10	Ketazolam
N05BA11	Prazepam
N05BA12	Alprazolam
N05BA13	Halazepam
N05BA14	Pinazepam
N05BA15	Camazepam
N05BA16	Nordazepam
N05BA17	Fludiazepam
N05BA18	Ethyl loflazepate
N05BA19	Etizolam
N05BA21	Clotiazepam
N05BA22	Cloxazolam
N05BA23	Tofisopam
N05BA24	Bentazepam
N06AA09	Amitriptyline
N06AX16	Venlafaxine
N06AX23	Desvenlafaxine

Table 56: Teratogens

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
A01AB04	amphotericin	Stomatological preparations	Alimentary tract and metabolism
A01AB08	neomycin	Stomatological preparations	Alimentary tract and metabolism
A01AB13	tetracycline	Stomatological preparations	Alimentary tract and metabolism
A01AB21	chlortetracycline	Stomatological preparations	Alimentary tract and metabolism
A01AB22	doxycycline	Stomatological preparations	Alimentary tract and metabolism

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
A01AB23	minocycline	Stomatological preparations	Alimentary tract and metabolism
A01AD05	aspirin = acetylsalicylic acid	Stomatological preparations	Alimentary tract and metabolism
A02BA04	nizatidine	Drugs for acid related disorders	Alimentary tract and metabolism
A02BB01	misoprostol	Drugs for acid related disorders	Alimentary tract and metabolism
A02BC01	omeprazole	Drugs for acid related disorders	Alimentary tract and metabolism
A02BC02	pantoprazole	Drugs for acid related disorders	Alimentary tract and metabolism
A02BC03	lansoprazole	Drugs for acid related disorders	Alimentary tract and metabolism
A02BC05	esomeprazole	Drugs for acid related disorders	Alimentary tract and metabolism
A03AD01	papaverine	Drugs for functional gastrointestinal disorders	Alimentary tract and metabolism
A04AA03	tropisetron	Antiemetics and antinauseants	Alimentary tract and metabolism
A04AA55	netupitant and palonosetron = palonosetron, combinations	Antiemetics and antinauseants	Alimentary tract and metabolism
A05AA01	chenodeoxycholic acid	Bile and liver therapy	Alimentary tract and metabolism
A05AA02	ursodeoxycholic acid	Bile and liver therapy	Alimentary tract and metabolism
A06AX06	tegaserod	Drugs for constipation	Alimentary tract and metabolism
A07AA01	neomycin	Intestinal antiinfectives	Alimentary tract and metabolism
A07AA04	streptomycin	Intestinal antiinfectives	Alimentary tract and metabolism
A07AA07	amphotericin	Intestinal antiinfectives	Alimentary tract and metabolism
A07AA08	kanamycin	Intestinal antiinfectives	Alimentary tract and metabolism

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
A07DA01	diphenoxylate	Antipropulsives	Alimentary tract and metabolism
A07DA03	loperamide	Antipropulsives	Alimentary tract and metabolism
A07EA04	betamethasone valerate = betamethasone acetate	Intestinal antiinflammatory agents	Alimentary tract and metabolism
A07EA06	budesonide = desonide	Intestinal antiinflammatory agents	Alimentary tract and metabolism
A07EA07	beclometasone = beclomethasone	Intestinal antiinflammatory agents	Alimentary tract and metabolism
A07EC02	mesalazine	Intestinal antiinflammatory agents	Alimentary tract and metabolism
A07EC03	olsalazine	Intestinal antiinflammatory agents	Alimentary tract and metabolism
A07EC04	balsalazide	Intestinal antiinflammatory agents	Alimentary tract and metabolism
A08AA04	dexfenfluramine	Antiobesity preparations, excl. Diet products	Alimentary tract and metabolism
A08AA05	mazindol	Antiobesity preparations, excl. Diet products	Alimentary tract and metabolism
A08AA10	sibutramine	Antiobesity preparations, excl. Diet products	Alimentary tract and metabolism
A10AB06	insulin glulisine	Drugs used in diabetes	Alimentary tract and metabolism
A10AD06	insulin aspart and insulin degludec	Drugs used in diabetes	Alimentary tract and metabolism
A10AE04	insulin glargine	Drugs used in diabetes	Alimentary tract and metabolism
A10AE54	insulin glargine and lixisenatide	Drugs used in diabetes	Alimentary tract and metabolism
A10BA02	metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BB01	glibenclamide	Drugs used in diabetes	Alimentary tract and metabolism
A10BB02	chlorpropamide	Drugs used in diabetes	Alimentary tract and metabolism

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
A10BB03	tolbutamide	Drugs used in diabetes	Alimentary tract and metabolism
A10BB05	tolazamide	Drugs used in diabetes	Alimentary tract and metabolism
A10BB07	glipizide	Drugs used in diabetes	Alimentary tract and metabolism
A10BB09	gliclazide	Drugs used in diabetes	Alimentary tract and metabolism
A10BB12	glimepiride	Drugs used in diabetes	Alimentary tract and metabolism
A10BD03	rosiglitazone and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD07	sitagliptin and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD08	vildagliptin and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD10	saxagliptin and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD11	linagliptin and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD13	alogliptin and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD15	dapagliflozin and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD19	empagliflozin and linagliptin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD20	empagliflozin and metformin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD21	dapagliflozin and saxagliptin	Drugs used in diabetes	Alimentary tract and metabolism
A10BD23	ertugliflozin pyroglutamic acid and metformin hydrochloride = metformin and ertugliflozin	Drugs used in diabetes	Alimentary tract and metabolism

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
A10BD24	ertugliflozin pyroglutamic acid and sitagliptin phosphate monohydrate = sitagliptin and ertugliflozin	Drugs used in diabetes	Alimentary tract and metabolism
A10BF01	acarbose	Drugs used in diabetes	Alimentary tract and metabolism
A10BF02	miglitol	Drugs used in diabetes	Alimentary tract and metabolism
A10BG01	troglitazone	Drugs used in diabetes	Alimentary tract and metabolism
A10BG02	rosiglitazone	Drugs used in diabetes	Alimentary tract and metabolism
A10BG03	pioglitazone	Drugs used in diabetes	Alimentary tract and metabolism
A10BH01	sitagliptin	Drugs used in diabetes	Alimentary tract and metabolism
A10BH02	vildagliptin	Drugs used in diabetes	Alimentary tract and metabolism
A10BH03	saxagliptin	Drugs used in diabetes	Alimentary tract and metabolism
A10BH04	alogliptin benzoate = alogliptin	Drugs used in diabetes	Alimentary tract and metabolism
A10BH05	linagliptin	Drugs used in diabetes	Alimentary tract and metabolism
A10BJ01	exenatide	Drugs used in diabetes	Alimentary tract and metabolism
A10BJ02	liraglutide	Drugs used in diabetes	Alimentary tract and metabolism
A10BJ05	dulaglutide	Drugs used in diabetes	Alimentary tract and metabolism
A10BJ06	semaglutide	Drugs used in diabetes	Alimentary tract and metabolism
A10BK01	dapagliflozin	Drugs used in diabetes	Alimentary tract and metabolism
A10BK02	canagliflozin	Drugs used in diabetes	Alimentary tract and metabolism

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
A10BK03	empagliflozin	Drugs used in diabetes	Alimentary tract and metabolism
A10BK04	ertugliflozin pyroglutamic acid = ertugliflozin	Drugs used in diabetes	Alimentary tract and metabolism
A10BX02	repaglinide	Drugs used in diabetes	Alimentary tract and metabolism
A10BX03	nateglinide	Drugs used in diabetes	Alimentary tract and metabolism
A11CA01	retinol = retinol (vit A)	Vitamins	Alimentary tract and metabolism
A11CC02	dihydrotachysterol	Vitamins	Alimentary tract and metabolism
A11CC04	calcitriol	Vitamins	Alimentary tract and metabolism
A14AA02	stanozolol	Anabolic agents for systemic use	Alimentary tract and metabolism
A14AA03	methandrostenolone = metandienone	Anabolic agents for systemic use	Alimentary tract and metabolism
A14AA04	metenolone	Anabolic agents for systemic use	Alimentary tract and metabolism
A14AA05	oxymetholone	Anabolic agents for systemic use	Alimentary tract and metabolism
A14AA07	prasteron	Anabolic agents for systemic use	Alimentary tract and metabolism
A14AA08	oxandrolone	Anabolic agents for systemic use	Alimentary tract and metabolism
A14AA09	norethandrolone	Anabolic agents for systemic use	Alimentary tract and metabolism
A14AB01	nandrolone	Anabolic agents for systemic use	Alimentary tract and metabolism
A16AA04	mercaptamine bitartrate = mercaptamine = cysteamine bitartrate	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AB01	alglucerase	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AB08	galsulfase	Other alimentary tract and metabolism products	Alimentary tract and metabolism

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
A16AB12	elosulfase alfa	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AB13	asfotase alfa	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AX03	sodium phenylbutyrate	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AX04	nitisinone	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AX06	miglustat	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AX10	eliglustat	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AX14	migalastat hydrochloride = migalastat	Other alimentary tract and metabolism products	Alimentary tract and metabolism
A16AX15	telotristat ethyl etiprate = telotristat	Other alimentary tract and metabolism products	Alimentary tract and metabolism
B01AA01	dicoumarol	Antithrombotic agents	Blood and blood forming organs
B01AA02	phenindione	Antithrombotic agents	Blood and blood forming organs
B01AA03	warfarin	Antithrombotic agents	Blood and blood forming organs
B01AA04	phenprocoumon	Antithrombotic agents	Blood and blood forming organs
B01AA07	nicoumalone = acenocoumarol	Antithrombotic agents	Blood and blood forming organs
B01AA08	ethyl biscoumacetate	Antithrombotic agents	Blood and blood forming organs
B01AA09	clorindione	Antithrombotic agents	Blood and blood forming organs
B01AA10	diphenadione	Antithrombotic agents	Blood and blood forming organs
B01AA11	tioclomarol	Antithrombotic agents	Blood and blood forming organs
B01AA12	fluindione	Antithrombotic agents	Blood and blood forming organs

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
B01AB01	heparin	Antithrombotic agents	Blood and blood forming organs
B01AB02	antithrombin iii	Antithrombotic agents	Blood and blood forming organs
B01AB04	dalteparin	Antithrombotic agents	Blood and blood forming organs
B01AB05	enoxaparin	Antithrombotic agents	Blood and blood forming organs
B01AB06	nadroparin	Antithrombotic agents	Blood and blood forming organs
B01AB09	danaparoid	Antithrombotic agents	Blood and blood forming organs
B01AB10	tinzaparin	Antithrombotic agents	Blood and blood forming organs
B01AC06	aspirin = acetylsalicylic acid	Antithrombotic agents	Blood and blood forming organs
B01AC11	iloprost	Antithrombotic agents	Blood and blood forming organs
B01AC13	abciximab	Antithrombotic agents	Blood and blood forming organs
B01AC16	eptifibatide	Antithrombotic agents	Blood and blood forming organs
B01AC21	treprostinil	Antithrombotic agents	Blood and blood forming organs
B01AC23	cilostazol	Antithrombotic agents	Blood and blood forming organs
B01AC30	aspirin and dipyridamole	Antithrombotic agents	Blood and blood forming organs
B01AD01	streptokinase	Antithrombotic agents	Blood and blood forming organs
B01AD03	anistreplase	Antithrombotic agents	Blood and blood forming organs
B01AD07	reteplase	Antithrombotic agents	Blood and blood forming organs
B01AD10	drotrecogin alfa	Antithrombotic agents	Blood and blood forming organs

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
B01AD11	tenecteplase	Antithrombotic agents	Blood and blood forming organs
B01AE01	desirudin	Antithrombotic agents	Blood and blood forming organs
B01AE02	lepirudin	Antithrombotic agents	Blood and blood forming organs
B01AE05	ximelagatran	Antithrombotic agents	Blood and blood forming organs
B01AE06	bivalirudin	Antithrombotic agents	Blood and blood forming organs
B01AE07	dabigatran etexilate	Antithrombotic agents	Blood and blood forming organs
B01AF01	rivaroxaban	Antithrombotic agents	Blood and blood forming organs
B01AF02	apixaban	Antithrombotic agents	Blood and blood forming organs
B01AX05	fondaparinux	Antithrombotic agents	Blood and blood forming organs
B02AA01	aminocaproic acid	Antihemorrhagics	Blood and blood forming organs
B02BD04	efraloctocog alfa (rhu) = coagulation factor IX = factor ix (human)	Antihemorrhagics	Blood and blood forming organs
B02BX05	eltrombopag	Antihemorrhagics	Blood and blood forming organs
B03AB05	ferric carboxymaltose = ferric oxide polymaltose complexes	Antianemic preparations	Blood and blood forming organs
B03AC	ferric derisomaltose (parenteral) = iron sucrose (parenteral) = Iron, parenteral preparations	Antianemic preparations	Blood and blood forming organs
B03AC01	ferric oxide polymaltose complexes	Antianemic preparations	Blood and blood forming organs
B03AC02	saccharated iron oxide	Antianemic preparations	Blood and blood forming organs

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
B03AC03	iron-sorbitol-citric acid complex	Antianemic preparations	Blood and blood forming organs
B03AC05	ferric sorbitol gluconic acid complex	Antianemic preparations	Blood and blood forming organs
B03AC06	ferric oxide dextran complexes	Antianemic preparations	Blood and blood forming organs
B03AC07	ferric sodium gluconate complex	Antianemic preparations	Blood and blood forming organs
B03AD04	ferric carboxymaltose = ferric oxide polymaltose complexes	Antianemic preparations	Blood and blood forming organs
B03XA01	erythropoietin	Antianemic preparations	Blood and blood forming organs
B03XA02	epoetin alfa = darbepoetin alfa	Antianemic preparations	Blood and blood forming organs
B03XA03	epoetin beta = methoxy polyethylene glycol-epoetin beta	Antianemic preparations	Blood and blood forming organs
B05AA06	gelatin - succinylated = gelatin agents	Blood substitutes and perfusion solutions	Blood and blood forming organs
B05AA07	pentastarch = hydroxyethylstarch	Blood substitutes and perfusion solutions	Blood and blood forming organs
B05CA04	sulfamethizole	Blood substitutes and perfusion solutions	Blood and blood forming organs
B05CA09	neomycin	Blood substitutes and perfusion solutions	Blood and blood forming organs
B06AC02	icatibant	Other hematological agents	Blood and blood forming organs
C01BA01	quinidine	Cardiac therapy	Cardiovascular system
C01BC04	flecainide	Cardiac therapy	Cardiovascular system
C01BD01	amiodarone	Cardiac therapy	Cardiovascular system
C01BD02	bretylium tosilate	Cardiac therapy	Cardiovascular system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
C01BD04	dofetilide	Cardiac therapy	Cardiovascular system
C01BD05	ibutilide	Cardiac therapy	Cardiovascular system
C01BD07	dronedarone	Cardiac therapy	Cardiovascular system
C01CA04	dopamine	Cardiac therapy	Cardiovascular system
C01CA09	metaraminol	Cardiac therapy	Cardiovascular system
C01CE02	milrinone	Cardiac therapy	Cardiovascular system
C01DX16	nicorandil	Cardiac therapy	Cardiovascular system
C01EB03	indometacin = indomethacin	Cardiac therapy	Cardiovascular system
C01EB16	ibuprofen	Cardiac therapy	Cardiovascular system
C01EB17	ivabradine	Cardiac therapy	Cardiovascular system
C02AC01	clonidine	Antihypertensives	Cardiovascular system
C02AC02	guanfacine hydrochloride = guanfacine	Antihypertensives	Cardiovascular system
C02AC05	moxonidine	Antihypertensives	Cardiovascular system
C02CA04	doxazosin	Antihypertensives	Cardiovascular system
C02DA01	diazoxide	Antihypertensives	Cardiovascular system
C02DB02	hydralazine	Antihypertensives	Cardiovascular system
C02DC01	minoxidil	Antihypertensives	Cardiovascular system
C02DD01	sodium nitroprusside = nitroprusside	Antihypertensives	Cardiovascular system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
C02KX01	bosentan	Antihypertensives	Cardiovascular system
C02KX02	ambrisentan	Antihypertensives	Cardiovascular system
C02KX03	sitaxentan	Antihypertensives	Cardiovascular system
C02KX04	macitentan	Antihypertensives	Cardiovascular system
C02KX05	riociguat	Antihypertensives	Cardiovascular system
C03AA01	bendrofluazide = bendroflumethiazide	Diuretics	Cardiovascular system
C03AA03	hydrochlorothiazide	Diuretics	Cardiovascular system
C03AA04	chlorothiazide	Diuretics	Cardiovascular system
C03AA07	cyclopenthiazide	Diuretics	Cardiovascular system
C03AA08	methyclothiazide	Diuretics	Cardiovascular system
C03AX01	valsartan and hydrochlorothiazide = hydrochlorothiazide, combinations	Diuretics	Cardiovascular system
C03BA02	quinethazone	Diuretics	Cardiovascular system
C03BA03	clopamide	Diuretics	Cardiovascular system
C03BA04	chlortalidone	Diuretics	Cardiovascular system
C03BA05	mefruside	Diuretics	Cardiovascular system
C03BA08	metolazone	Diuretics	Cardiovascular system
C03BA11	indapamide	Diuretics	Cardiovascular system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
C03CA01	frusemide = furosemide	Diuretics	Cardiovascular system
C03CA02	bumetanide	Diuretics	Cardiovascular system
C03CC01	etacrynic acid	Diuretics	Cardiovascular system
C03DA01	spironolactone	Diuretics	Cardiovascular system
C03DA04	eplerenone	Diuretics	Cardiovascular system
C03DB01	amiloride	Diuretics	Cardiovascular system
C03DB02	triamterene	Diuretics	Cardiovascular system
C03XA01	tolvaptan	Diuretics	Cardiovascular system
C04AA01	isoxsuprine	Peripheral vasodilators	Cardiovascular system
C04AD03	oxpentifylline = pentoxifylline	Peripheral vasodilators	Cardiovascular system
C05AA05	betamethasone valerate = betamethasone acetate	Vasoprotectives	Cardiovascular system
C05AA06	fluorometholone	Vasoprotectives	Cardiovascular system
C05AA12	triamcinolone	Vasoprotectives	Cardiovascular system
C05AE03	diltiazem	Vasoprotectives	Cardiovascular system
C05BA03	heparin	Vasoprotectives	Cardiovascular system
C05BB02	lauromacrogol = polidocanol	Vasoprotectives	Cardiovascular system
C07AA01	alprenolol	Beta blocking agents	Cardiovascular system
C07AA02	oxprenolol	Beta blocking agents	Cardiovascular system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
C07AA03	pindolol	Beta blocking agents	Cardiovascular system
C07AA05	propranolol	Beta blocking agents	Cardiovascular system
C07AA06	timolol	Beta blocking agents	Cardiovascular system
C07AA07	sotalol	Beta blocking agents	Cardiovascular system
C07AB02	metoprolol	Beta blocking agents	Cardiovascular system
C07AB03	atenolol	Beta blocking agents	Cardiovascular system
C07AB05	betaxolol	Beta blocking agents	Cardiovascular system
C07AB06	bevantolol	Beta blocking agents	Cardiovascular system
C07AB07	bisoprolol	Beta blocking agents	Cardiovascular system
C07AB09	esmolol	Beta blocking agents	Cardiovascular system
C07AB12	nebivolol	Beta blocking agents	Cardiovascular system
C07AG01	labetalol	Beta blocking agents	Cardiovascular system
C07AG02	carvedilol	Beta blocking agents	Cardiovascular system
C08CA01	amlodipine	Calcium channel blockers	Cardiovascular system
C08CA02	felodipine	Calcium channel blockers	Cardiovascular system
C08CA03	isradipine	Calcium channel blockers	Cardiovascular system
C08CA04	nicardipine	Calcium channel blockers	Cardiovascular system
C08CA05	nifedipine	Calcium channel blockers	Cardiovascular system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
C08CA06	nimodipine	Calcium channel blockers	Cardiovascular system
C08CA07	nisoldipine	Calcium channel blockers	Cardiovascular system
C08CA13	lercanidipine	Calcium channel blockers	Cardiovascular system
C08CA16	clevidipine	Calcium channel blockers	Cardiovascular system
C08DA01	verapamil	Calcium channel blockers	Cardiovascular system
C08DB01	diltiazem	Calcium channel blockers	Cardiovascular system
C09AA01	captopril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA02	enalapril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA03	lisinopril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA04	perindopril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA05	ramipril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA06	quinapril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA07	benazepril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA08	cilazapril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA09	fosinopril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09AA10	trandolapril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09CA01	losartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09CA02	eprosartan	Agents acting on the renin-angiotensin system	Cardiovascular system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
C09CA03	valsartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09CA04	irbesartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09CA06	candesartan cilexetil = candesartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09CA07	telmisartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09CA08	olmesartan medoxomil = olmesartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09DB01	valsartan and amlodipine	Agents acting on the renin-angiotensin system	Cardiovascular system
C09DB02	amlodipine and olmesartan medoxomil	Agents acting on the renin-angiotensin system	Cardiovascular system
C09DB04	amlodipine and telmisartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09DX01	amlodipine and hydrochlorothiazide and valsartan	Agents acting on the renin-angiotensin system	Cardiovascular system
C09DX03	amlodipine, olmesartan medoxomil and hydrochlorothiazide	Agents acting on the renin-angiotensin system	Cardiovascular system
C09DX04	valsartan and sacubitril	Agents acting on the renin-angiotensin system	Cardiovascular system
C09XA02	aliskiren	Agents acting on the renin-angiotensin system	Cardiovascular system
C10AA01	simvastatin	Lipid modifying agents	Cardiovascular system
C10AA02	lovastatin	Lipid modifying agents	Cardiovascular system
C10AA03	pravastatin	Lipid modifying agents	Cardiovascular system
C10AA04	fluvastatin	Lipid modifying agents	Cardiovascular system
C10AA05	atorvastatin	Lipid modifying agents	Cardiovascular system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
C10AA06	cerivastatin	Lipid modifying agents	Cardiovascular system
C10AA07	rosuvastatin	Lipid modifying agents	Cardiovascular system
C10AA08	pitavastatin	Lipid modifying agents	Cardiovascular system
C10AB04	gemfibrozil	Lipid modifying agents	Cardiovascular system
C10AB05	fenofibrate	Lipid modifying agents	Cardiovascular system
C10AX09	ezetimibe	Lipid modifying agents	Cardiovascular system
C10BA05	atorvastatin and ezetimibe	Lipid modifying agents	Cardiovascular system
C10BA06	rosuvastatin and ezetimibe	Lipid modifying agents	Cardiovascular system
C10BX03	amlodipine and atorvastatin	Lipid modifying agents	Cardiovascular system
D01AA08	griseofulvin	Antifungals for dermatological use	Dermatologicals
D01AC04	chlormidazole	Antifungals for dermatological use	Dermatologicals
D01AC06	tiabendazole	Antifungals for dermatological use	Dermatologicals
D01AC07	tioconazole	Antifungals for dermatological use	Dermatologicals
D01AC08	ketoconazole	Antifungals for dermatological use	Dermatologicals
D01AC09	sulconazole	Antifungals for dermatological use	Dermatologicals
D01AC10	bifonazole	Antifungals for dermatological use	Dermatologicals
D01AC11	oxiconazole	Antifungals for dermatological use	Dermatologicals
D01AC12	fenticonazole	Antifungals for dermatological use	Dermatologicals

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
D01AC13	omoconazole	Antifungals for dermatological use	Dermatologicals
D01AC14	sertaconazole	Antifungals for dermatological use	Dermatologicals
D01AC15	fluconazole	Antifungals for dermatological use	Dermatologicals
D01AC16	flutrimazole	Antifungals for dermatological use	Dermatologicals
D01AC17	eberconazole	Antifungals for dermatological use	Dermatologicals
D01AC18	luliconazole	Antifungals for dermatological use	Dermatologicals
D01AC19	efinaconazole	Antifungals for dermatological use	Dermatologicals
D01AE14	ciclopirox	Antifungals for dermatological use	Dermatologicals
D01AE16	amorolfine	Antifungals for dermatological use	Dermatologicals
D01AE21	flucytosine	Antifungals for dermatological use	Dermatologicals
D01BA01	griseofulvin	Antifungals for dermatological use	Dermatologicals
D04AA10	promethazine	Antihistamines for topical use	Dermatologicals
D04AB03	oxybuprocaine	Antihistamines for topical use	Dermatologicals
D04AX01	doxepin	Antihistamines for topical use	Dermatologicals
D05AD02	methoxsalen	Antipsoriatics	Dermatologicals
D05AX05	tazarotene	Antipsoriatics	Dermatologicals
D05BB01	etretinate	Antipsoriatics	Dermatologicals
D05BB02	acitretin	Antipsoriatics	Dermatologicals
D06AA01	demeclocycline	Antibiotics for topical use	Dermatologicals
D06AA02	chlortetracycline	Antibiotics for topical use	Dermatologicals
D06AA03	oxytetracycline	Antibiotics for topical use	Dermatologicals

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
D06AA04	tetracycline	Antibiotics for topical use	Dermatologicals
D06AX01	sodium fusidate = fusidic acid	Antibiotics for topical use	Dermatologicals
D06AX04	neomycin	Antibiotics for topical use	Dermatologicals
D06AX07	gentamicin	Antibiotics for topical use	Dermatologicals
D06AX12	amikacin	Antibiotics for topical use	Dermatologicals
D06BA04	sulfamethizole	Chemotherapeutics for topical use	Dermatologicals
D06BB01	idoxuridine	Chemotherapeutics for topical use	Dermatologicals
D06BB03	aciclovir	Chemotherapeutics for topical use	Dermatologicals
D06BB04	podophyllotoxin	Chemotherapeutics for topical use	Dermatologicals
D06BX02	ingenol = ingenol mebutate	Chemotherapeutics for topical use	Dermatologicals
D07AA01	methylprednisolone aceponate	Corticosteroids, dermatological preparations	Dermatologicals
D07AB06	fluorometholone	Corticosteroids, dermatological preparations	Dermatologicals
D07AB08	Desonide	Corticosteroids, dermatological preparations	Dermatologicals
D07AC01	betamethasone valerate = betamethasone acetate	Corticosteroids, dermatological preparations	Dermatologicals
D07AC09	budesonide = desonide	Corticosteroids, dermatological preparations	Dermatologicals
D07AC13	mometasone	Corticosteroids, dermatological preparations	Dermatologicals
D07AC15	beclometasone = beclomethasone	Corticosteroids, dermatological preparations	Dermatologicals

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
D07AC17	fluticasone propionate = fluticasone	Corticosteroids, dermatological preparations	Dermatologicals
D07XB04	fluorometholone	Corticosteroids, dermatological preparations	Dermatologicals
D07XC01	betamethasone valerate = betamethasone acetate	Corticosteroids, dermatological preparations	Dermatologicals
D07XC03	mometasone	Corticosteroids, dermatological preparations	Dermatologicals
D09AA01	framycetin	Medicated dressings	Dermatologicals
D09AA02	sodium fusidate = fusidic acid	Medicated dressings	Dermatologicals
D09AA13	iodoform	Medicated dressings	Dermatologicals
D10AA01	fluorometholone	Anti-acne preparations	Dermatologicals
D10AA02	methylprednisolone aceponate	Anti-acne preparations	Dermatologicals
D10AD01	tretinoin	Anti-acne preparations	Dermatologicals
D10AD02	retinol	Anti-acne preparations	Dermatologicals
D10AD03	adapalene	Anti-acne preparations	Dermatologicals
D10AD04	isotretinoin	Anti-acne preparations	Dermatologicals
D10AE51	benzoyl peroxide and adapalene	Anti-acne preparations	Dermatologicals
D10AF06	sulfacetamide	Anti-acne preparations	Dermatologicals
D10AF51	clindamycin and tretinoin	Anti-acne preparations	Dermatologicals
D10BA01	isotretinoin	Anti-acne preparations	Dermatologicals
D11AE01	methandrostenolone = metandienone	Other dermatological preparations	Dermatologicals
D11AH01	tacrolimus	Other dermatological preparations	Dermatologicals
D11AH02	pimecrolimus	Other dermatological preparations	Dermatologicals
D11AH04	alitretinoin	Other dermatological preparations	Dermatologicals

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
D11AX01	minoxidil	Other dermatological preparations	Dermatologicals
D11AX10	finasteride	Other dermatological preparations	Dermatologicals
D11AX16	eflornithine	Other dermatological preparations	Dermatologicals
D11AX18	diclofenac	Other dermatological preparations	Dermatologicals
D11AX22	ivermectin	Other dermatological preparations	Dermatologicals
G01AA03	amphotericin	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AA07	oxytetracycline	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AE10	combination of sulfonamides	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AF08	tioconazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AF11	ketoconazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AF12	fenticonazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AF15	butoconazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AF16	omoconazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AF17	oxiconazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G01AF18	flutrimazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AF19	sertaconazole	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G01AX12	ciclopirox	Gynecological antiinfectives and antiseptics	Genito urinary system and sex hormones
G02AB03	ergometrine	Uterotonics	Genito urinary system and sex hormones
G02AD01	dinoprost	Uterotonics	Genito urinary system and sex hormones
G02AD02	dinoprostone prostaglandin e2 = dinoprostone	Uterotonics	Genito urinary system and sex hormones
G02AD03	gemeprost	Uterotonics	Genito urinary system and sex hormones
G02AD04	carboprost	Uterotonics	Genito urinary system and sex hormones
G02CB04	quinagolide	Other gynecologicals	Genito urinary system and sex hormones
G02CC01	ibuprofen	Other gynecologicals	Genito urinary system and sex hormones
G02CC02	naproxen	Other gynecologicals	Genito urinary system and sex hormones
G03AA01	etynodiol and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA02	quingestanol and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA03	lynestrenol and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA04	megestrol and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G03AA05	norethisterone and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA06	norgestrel and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA07	levonorgestrel and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA08	medroxyprogesterone and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA09	desogestrel and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA10	gestodene and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA11	norgestimate and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA12	drospirenone and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA13	norelgestromin and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA14	nomegestrol and estradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA15	chlormadinone and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA16	dienogest and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AA17	medroxyprogesterone and estradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G03AB01	megestrol and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB02	lynestrenol and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB03	levonorgestrel and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB04	norethisterone and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB05	desogestrel and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB06	gestodene and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB07	chlormadinone and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB08	dienogest and estradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AB09	norgestimate and ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC01	norethisterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC02	lynestrenol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC03	levonorgestrel	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC04	quingestanol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G03AC05	megestrol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC06	medroxyprogesterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC07	norgestrienone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC08	etonogestrel	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC09	desogestrel	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AC10	drospirenone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AD01	levonorgestrel	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03AD02	ulipristal	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03BA01	fluoxymesterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03BA02	methyltestosterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03BA03	testosterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03BB01	mesterolon	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03CA01	ethinylestradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G03CA03	estradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03CA57	estrogens,esterified = conjugated estrogens	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03CB01	dienoestrol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03CB02	diethylstilbestrol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03CC02	dienoestrol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03CC05	diethylstilbestrol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03CX01	tibolone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DA02	medroxyprogesterone = medrogestone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DA03	hydroxyprogesterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DA04	progesterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DB01	dydrogesteron	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DB02	megestrol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DB03	medrogestron	Sex hormones and modulators of the genital system	genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G03DB04	nomegestrol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DC02	norethisterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03DC03	lynestrenol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03EK01	methyltestosterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03FA12	medroxyprogesterone and estrogen	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03FA14	dydrogesterone and estradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03FB06	medroxyprogesterone and estrogen	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03FB08	dydrogesterone and estradiol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03GA02	gonadotrophin - human menopausal	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03GA04	follicle stimulating hormone (recombinant human) = urofollitropin	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03GA05	follicle stimulating hormone (recombinant human) = follitropin alfa	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03GA07	lutropin alfa	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03GA08	choriogonadotropin alfa	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G03GA09	follicle stimulating hormone (recombinant human) = corifollitropin alfa	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03GA10	follicle stimulating hormone (recombinant human) = follitropin delta	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03GB02	clomifene	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03HA01	cyproterone acetate (10 mg daily or higher po) = cyproterone acetate (2 mg daily po) = cyproterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03XA01	danazol	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03XA02	gestrinon	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03XB02	ulipristal	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03XC01	raloxifene	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G03XX01	prasterone	Sex hormones and modulators of the genital system	Genito urinary system and sex hormones
G04BD07	tolterodine	Urologicals	Genito urinary system and sex hormones
G04BD08	solifenacin	Urologicals	Genito urinary system and sex hormones
G04BD10	darifenacin	Urologicals	Genito urinary system and sex hormones
G04BD12	mirabegron	Urologicals	Genito urinary system and sex hormones
G04BE02	papaverine	Urologicals	Genito urinary system and sex hormones

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
G04BE07	apomorphine	Urologicals	Genito urinary system and sex hormones
G04BE09	vardenafil	Urologicals	Genito urinary system and sex hormones
G04BX03	acetohydroxamic acid	Urologicals	Genito urinary system and sex hormones
G04BX14	dapoxetine	Urologicals	Genito urinary system and sex hormones
G04CA04	silodosin	Urologicals	Genito urinary system and sex hormones
G04CB01	finasteride	Urologicals	Genito urinary system and sex hormones
G04CB02	dutasteride	Urologicals	Genito urinary system and sex hormones
H01AA02	tetracosactide	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01AC06	tesamorelin	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01AX01	pegvisomant	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01BA04	terlipressin	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01BA05	ornipressin	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01BB03	carbetocin	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
H01CA02	nafarelin	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01CB02	octreotide	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01CB03	lanreotide	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01CB05	pasireotide diaspartate = pasireotide embonate	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01CC01	ganirelix	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H01CC02	cetrorelix	Pituitary and hypothalamic hormones and analogues	Systemic hormonal preparations, excl. sex hormones and insulins
H02AA02	fludrocortisone	Corticosteroids for systemic use	Systemic hormonal preparations, excl. sex hormones and insulins
H02AB01	betamethasone valerate = betamethasone acetate	Corticosteroids for systemic use	Systemic hormonal preparations, excl. sex hormones and insulins
H02AB04	methylprednisolone aceponate	Corticosteroids for systemic use	Systemic hormonal preparations, excl. sex hormones and insulins
H02AB08	triamcinolone	Corticosteroids for systemic use	Systemic hormonal preparations, excl. sex hormones and insulins

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
H03BA02	propylthiouracil	Thyroid therapy	Systemic hormonal preparations, excl. sex hormones and insulins
H03BB01	carbimazole	Thyroid therapy	Systemic hormonal preparations, excl. sex hormones and insulins
H03BB02	methimazole = thiamazole	Thyroid therapy	Systemic hormonal preparations, excl. sex hormones and insulins
H04AA01	glucagon	Pancreatic hormones	Systemic hormonal preparations, excl. Sex hormones and insulins
H05AA02	teriparatide	Calcium homeostasis	Systemic hormonal preparations, excl. sex hormones and insulins
H05BX01	cinacalcet	Calcium homeostasis	Systemic hormonal preparations, excl. sex hormones and insulins
H05BX02	paricalcitol	Calcium homeostasis	Systemic hormonal preparations, excl. sex hormones and insulins
J01AA01	demeclocycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA02	doxycycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA03	chlortetracycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA04	lymecycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA05	metacycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA06	oxytetracycline	Antibacterials for systemic use	Antiinfectives for systemic use

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
J01AA07	tetracycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA08	minocycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA09	rolitetracycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA10	penimepicycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA11	clomocycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA12	tigecycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA13	eravacycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA14	sarecycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01AA15	omadacycline	Antibacterials for systemic use	Antiinfectives for systemic use
J01CA09	azlocillin	Antibacterials for systemic use	Antiinfectives for systemic use
J01DH03	ertapenem	Antibacterials for systemic use	Antiinfectives for systemic use
J01DH51	imipenem and cilastatin	Antibacterials for systemic use	Antiinfectives for systemic use
J01EA01	trimethoprim	Antibacterials for systemic use	Antiinfectives for systemic use
J01EB02	sulfamethizole	Antibacterials for systemic use	Antiinfectives for systemic use
J01EC01	sulfamethoxazole	Antibacterials for systemic use	Antiinfectives for systemic use
J01EC02	sulfadiazine	Antibacterials for systemic use	Antiinfectives for systemic use
J01FA09	clarithromycin	Antibacterials for systemic use	Antiinfectives for systemic use
J01FG02	dalfopristin and quinupristin	Antibacterials for systemic use	Antiinfectives for systemic use

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
J01GA01	streptomycin	Antibacterials for systemic use	Antiinfectives for systemic use
J01GB01	tobramycin	Antibacterials for systemic use	Antiinfectives for systemic use
J01GB03	gentamicin	Antibacterials for systemic use	Antiinfectives for systemic use
J01GB04	kanamycin	Antibacterials for systemic use	Antiinfectives for systemic use
J01GB05	neomycin	Antibacterials for systemic use	Antiinfectives for systemic use
J01GB06	amikacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01GB07	netilmicin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA01	ofloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA02	ciprofloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA03	pefloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA04	enoxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA05	temafloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA06	norfloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA07	lomefloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA08	fleroxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA09	sparfloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA10	rufloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA11	grepafloxacin	Antibacterials for systemic use	Antiinfectives for systemic use

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
J01MA12	levofloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA13	alatrofloxacin= trovafloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA14	moxifloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA15	gemifloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA16	gatifloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA17	prulifloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA18	pazufloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA19	garenoxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA21	sitafloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA22	tosufloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MA23	delafloxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MB01	rosoxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MB02	nalidixic acid	Antibacterials for systemic use	Antiinfectives for systemic use
J01MB03	piromidic acid	Antibacterials for systemic use	Antiinfectives for systemic use
J01MB06	cinoxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01MB07	flumequine	Antibacterials for systemic use	Antiinfectives for systemic use
J01MB08	nemonoxacin	Antibacterials for systemic use	Antiinfectives for systemic use
J01XA02	teicoplanin	Antibacterials for systemic use	Antiinfectives for systemic use

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
J01XC01	sodium fusidate = fusidic acid	Antibacterials for systemic use	Antiinfectives for systemic use
J01XD02	tinidazole	Antibacterials for systemic use	Antiinfectives for systemic use
J01XX08	linezolid	Antibacterials for systemic use	Antiinfectives for systemic use
J02AA01	amphotericin	Antimycotics for systemic use	Antiinfectives for systemic use
J02AB02	ketoconazole	Antimycotics for systemic use	Antiinfectives for systemic use
J02AC01	fluconazole	Antimycotics for systemic use	Antiinfectives for systemic use
J02AC02	itraconazole	Antimycotics for systemic use	Antiinfectives for systemic use
J02AC03	voriconazole	Antimycotics for systemic use	Antiinfectives for systemic use
J02AC04	posaconazole	Antimycotics for systemic use	Antiinfectives for systemic use
J02AX01	flucytosine	Antimycotics for systemic use	Antiinfectives for systemic use
J02AX04	caspofungin	Antimycotics for systemic use	Antiinfectives for systemic use
J02AX05	micafungin	Antimycotics for systemic use	Antiinfectives for systemic use
J02AX06	anidulafungin	Antimycotics for systemic use	Antiinfectives for systemic use
J04AB02	rifampicin	Antimycobacterials	Antiinfectives for systemic use
J04AB04	rifabutin	Antimycobacterials	Antiinfectives for systemic use
J04BA01	clofazimine	Antimycobacterials	Antiinfectives for systemic use
J05AB01	aciclovir	Antivirals for systemic use	Antiinfectives for systemic use
J05AB06	ganciclovir	Antivirals for systemic use	Antiinfectives for systemic use

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
J05AB11	valaciclovir	Antivirals for systemic use	Antiinfectives for systemic use
J05AB12	cidofovir	Antivirals for systemic use	Antiinfectives for systemic use
J05AB14	valganciclovir	Antivirals for systemic use	Antiinfectives for systemic use
J05AD01	foscarnet	Antivirals for systemic use	Antiinfectives for systemic use
J05AE02	indinavir	Antivirals for systemic use	Antiinfectives for systemic use
J05AE03	ritonavir	Antivirals for systemic use	Antiinfectives for systemic use
J05AE05	amprenavir	Antivirals for systemic use	Antiinfectives for systemic use
J05AE07	fosamprenavir	Antivirals for systemic use	Antiinfectives for systemic use
J05AE09	tipranavir	Antivirals for systemic use	Antiinfectives for systemic use
J05AF01	zidovudine	Antivirals for systemic use	Antiinfectives for systemic use
J05AF03	zalcitabine	Antivirals for systemic use	Antiinfectives for systemic use
J05AF04	stavudine	Antivirals for systemic use	Antiinfectives for systemic use
J05AF05	lamivudine	Antivirals for systemic use	Antiinfectives for systemic use
J05AF06	abacavir	Antivirals for systemic use	Antiinfectives for systemic use
J05AF07	tenofovir = tenofovir disoproxil	Antivirals for systemic use	Antiinfectives for systemic use
J05AF08	adefovir	Antibacterials for systemic use	Antiinfectives for systemic use
J05AF10	entecavir	Antivirals for systemic use	Antiinfectives for systemic use
J05AF13	tenofovir = tenofovir alafenamide	Antivirals for systemic use	Antiinfectives for systemic use

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
J05AG01	nevirapine	Antivirals for systemic use	Antiinfectives for systemic use
J05AG02	delavirdine	Antivirals for systemic use	Antiinfectives for systemic use
J05AG03	efavirenz	Antivirals for systemic use	Antiinfectives for systemic use
J05AH03	peramivir	Antivirals for systemic use	Antiinfectives for systemic use
J05AP01	ribavirin	Antivirals for systemic use	Antiinfectives for systemic use
J05AP03	boceprevir and ribavirin and peginterferon alfa	Antivirals for systemic use	Antiinfectives for systemic use
J05AP05	simeprevir	Antivirals for systemic use	Antiinfectives for systemic use
J05AP07	daclatasvir	Antivirals for systemic use	Antiinfectives for systemic use
J05AP51	ledipasvir and sofosbuvir	Antivirals for systemic use	Antiinfectives for systemic use
J05AP52	paritaprevir, ritonavir, ombitasvir and dasabuvir	Antivirals for systemic use	Antiinfectives for systemic use
J05AP53	paritaprevir, ritonavir and ombitasvir	Antivirals for systemic use	Antiinfectives for systemic use
J05AR02	abacavir and lamivudine	Antivirals for systemic use	Antiinfectives for systemic use
J05AR03	emtricitabine and tenofovir disoproxil maleate	Antivirals for systemic use	Antiinfectives for systemic use
J05AR04	abacavir and lamivudine and zidovudine	Antivirals for systemic use	Antiinfectives for systemic use
J05AR08	emtricitabine and tenofovir disoproxil fumarate and rilpivirine	Antivirals for systemic use	Antiinfectives for systemic use
J05AR09	tenofovir disoproxil, emtricitabine, elvitegravir and cobicistat	Antivirals for systemic use	Antiinfectives for systemic use
J05AR10	lopinavir and ritonavir	Antivirals for systemic use	Antiinfectives for systemic use

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
J05AR13	abacavir, dolutegravir and lamivudine	Antivirals for systemic use	Antiinfectives for systemic use
J05AR17	emtricitabine and tenofovir alafenamide	Antivirals for systemic use	Antiinfectives for systemic use
J05AR18	elvitegravir, cobicistat, emtricitabine, tenofovir and alafenamide	Antivirals for systemic use	Antiinfectives for systemic use
J05AR19	emtricitabine, ripilvirine and tenofovir alafenamide	Antivirals for systemic use	Antiinfectives for systemic use
J05AR20	bictegravir, emtricitabine and tenofovir alafenamide	Antivirals for systemic use	Antiinfectives for systemic use
J05AX08	raltegravir	Antivirals for systemic use	Antiinfectives for systemic use
J05AX18	letermovir	Antivirals for systemic use	Antiinfectives for systemic use
J07BX01	smallpox (vaccinia) vaccine = smallpox, live attenuated	Vaccines	Antiinfectives for systemic use
L01AA01	cyclophosphamide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AA02	chlorambucil	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AA03	melphalan	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AA05	mechlorethamine = mustine = chlormethine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AA06	ifosfamide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AA09	bendamustine hydrochloride	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AB01	busulfan	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01AC01	thiotepa	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AD01	carmustine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AD02	lomustine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AD04	streptozocin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AD05	fotemustine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AX03	temozolomide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01AX04	dacarbazine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BA01	amethopterin = methotrexate	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BA03	raltitrexed	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BA04	pemetrexed	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BA05	pralatrexate	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BB02	mercaptopurine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BB03	tioguanine	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01BB04	cladribine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BB05	fludarabine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BB06	clofarabine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BB07	nelarabine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BC01	cytarabine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BC02	fluorouracil	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BC03	tegafur	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BC05	gemcitabine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BC06	capecitabine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BC07	azacitidine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01BC59	Trifluridine combinations	Antineoplastic agents	antineoplastic and immunomodulating agents
L01CA01	vinblastine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CA02	vincristine	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01CA03	vindesine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CA04	vinorelbine tartrate = vinorelbine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CA05	vinflunine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CB01	etoposide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CB02	teniposide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CD01	paclitaxel	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CD02	docetaxel	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01CD04	cabazitaxel	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01DA01	actinomycin d = dactinomycin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01DB01	doxorubicin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01DB02	daunorubicin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01DB03	epirubicin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01DB06	idarubicin	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01DB07	mitozantrone = mitoxantrone	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01DC01	bleomycin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01DC03	mitomycin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XA01	cisplatin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XA02	carboplatin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XA03	oxaliplatin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XB01	procarbazine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC02	rituximab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC03	trastuzumab emtansine = trastuzumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC06	cetuximab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC07	bevacizumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC08	panitumumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC10	ofatumumab	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01XC11	ipilimumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC12	brentuximab vedotin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC13	pertuzumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC15	obinutuzumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC17	nivolumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC18	pembrolizumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC19	blinatumomab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC21	ramucirumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC23	elotuzumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC24	daratumumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC26	inotuzumab ozogamicin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC28	durvalumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XC31	avelumab	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01XC32	atezolizumab	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XD04	aminolevulinic acid	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE01	imatinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE02	gefitinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE03	erlotinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE04	sunitinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE05	sorafenib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE06	dasatinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE07	lapatinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE08	nilotinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE09	temsirolimus	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE10	everolimus	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE11	pazopanib	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01XE13	afatinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE15	vemurafenib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE16	crizotinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE17	axitinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE18	ruxolitinib phosphate = ruxolitinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE21	regorafenib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE23	dabrafenib mesilate = dabrafenib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE24	ponatinib hydrochloride = ponatinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE25	trametinib dimethyl sulfoxide = trametinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE26	cabozantinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE27	ibrutinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE28	ceritinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE29	lenvatinib	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01XE31	nintedanib esilate = nintedanib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE33	palbociclib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE35	osimertinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE36	alectinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE38	cobimetinib fumarate = cobimetinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE39	midostaurin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE41	binimetinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE42	ribociclib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE45	neratinib maleate = neratinib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XE46	encorafenib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX01	amsacrine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX02	asparaginase = l-asparaginase = colaspase	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX03	altretamine hexamethylmelamine = altretamine	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01XX05	hydroxyurea = hydroxycarbamide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX08	pentostatin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX11	estramustine	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX14	tretinoin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX17	topotecan	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX19	irinotecan sucrosofate = irinotecan	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX22	alitretinoin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX24	pegaspargase	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX27	arsenic trioxide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX32	bortezomib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX33	celecoxib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX35	anagrelide	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX38	vorinostat	Antineoplastic agents	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L01XX39	romidepsin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX41	eribulin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX42	panobinostat	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX43	vismodegib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX44	aflibercept	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX45	carfilzomib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX46	olaparib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX47	idelalisib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX50	ixazomib	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX51	talimogene laherparepvec	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX52	venetoclax	Antineoplastic agents	Antineoplastic and immunomodulating agents
L01XX57	plitidepsin	Antineoplastic agents	Antineoplastic and immunomodulating agents
L02AA01	diethylstilbestrol	Endocrine therapy	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L02AA03	ethinylestradiol	Endocrine therapy	Antineoplastic and immunomodulating agents
L02AB01	megestrol	Endocrine therapy	Antineoplastic and immunomodulating agents
L02AB02	medroxyprogesterone = medrogestron im	Endocrine therapy	Antineoplastic and immunomodulating agents
L02AE01	buserelin	Endocrine therapy	Antineoplastic and immunomodulating agents
L02AE02	leuprorelin	Endocrine therapy	Antineoplastic and immunomodulating agents
L02AE03	goserelin	Endocrine therapy	Antineoplastic and immunomodulating agents
L02AE04	triptorelin	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BA01	tamoxifen	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BA02	toremifene	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BA03	fulvestrant	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BB03	bicalutamide	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BB04	enzalutamide	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BB05	apalutamide	Endocrine therapy	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L02BG01	aminoglutethimide	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BG02	formestane	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BG03	anastrozole	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BG04	letrozole	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BG06	exemestane	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BX02	degarelix	Endocrine therapy	Antineoplastic and immunomodulating agents
L02BX03	abiraterone	Endocrine therapy	Antineoplastic and immunomodulating agents
L03AA02	filgrastim	Immunostimulants	Antineoplastic and immunomodulating agents
L03AA03	molgramostim	Immunostimulants	Antineoplastic and immunomodulating agents
L03AA10	lenograstim	Immunostimulants	Antineoplastic and immunomodulating agents
L03AA13	pegfilgrastim	Immunostimulants	Antineoplastic and immunomodulating agents
L03AA14	lipegfilgrastim	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB03	interferon gamma-1b = interferon gamma	Immunostimulants	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L03AB04	interferon alpha-2a	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB05	interferon alpha-2b	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB07	interferon beta-1a	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB08	interferon beta 1b	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB10	peginterferon alfa-2b	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB11	peginterferon alfa-2a	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB13	peginterferon beta-1a	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB60	simeprevir and ribavirin and peginterferon alfa = peginterferon alfa-2b, combinations	Immunostimulants	Antineoplastic and immunomodulating agents
L03AB61	sofosbuvir and peginterferon alfa and ribavirin = peginterferon alfa-2a, combinations	Immunostimulants	Antineoplastic and immunomodulating agents
L03AC01	aldesleukin	Immunostimulants	Antineoplastic and immunomodulating agents
L03AX11	tasonermin	Immunostimulants	Antineoplastic and immunomodulating agents
L03AX16	plerixafor	Immunostimulants	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L04AA04	anti-thymocyte immunoglobulin	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA06	mycophenolate mofetil = mycophenolic acid	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA10	sirolimus	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA13	leflunomide	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA15	alefacept	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA18	everolimus	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA21	efalizumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA23	natalizumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA24	abatacept	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA26	belimumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA27	fingolimod	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA28	belatacept	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA29	tofacitinib citrate = tofacitinib	Immunosuppressants	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L04AA31	teriflunomide	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA32	apremilast	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA36	ocrelizumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA37	baricitinib	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AA40	cladribine	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AB01	etanercept	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AB02	infliximab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AB04	adalimumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AB05	certolizumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AB06	golimumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AC01	daclizumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AC02	basiliximab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AC07	tocilizumab	Immunosuppressants	Antineoplastic and immunomodulating agents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
L04AC08	canakinumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AC10	secukinumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AC11	siltuximab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AC13	ixekizumab	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AD01	ciclosporin	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AD02	tacrolimus	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AX01	azathioprine	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AX02	thalidomide	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AX03	methotrexate	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AX04	lenalidomide	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AX05	pirfenidone	Immunosuppressants	Antineoplastic and immunomodulating agents
L04AX06	pomalidomide	Immunosuppressants	Antineoplastic and immunomodulating agents
M01AA01	phenylbutazone	Antiinflammatory and antirheumatic products	Musculo-skeletal system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
M01AB01	indometacin = indomethacin	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AB02	sulindac	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AB05	diclofenac	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AB15	ketorolac	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AC01	piroxicam	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AC02	tenoxicam	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AC06	meloxicam	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AE01	ibuprofen	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AE02	naproxen	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AE03	ketoprofen	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AE11	tiaprofenic acid	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AG01	mefenamic acid	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AH01	celecoxib	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AH02	rofecoxib	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AH03	valdecoxib	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AH04	parecoxib	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AH05	etoricoxib	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01AH06	lumiracoxib	Antiinflammatory and antirheumatic products	Musculo-skeletal system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
M01AX01	nabumetone	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01CB03	auranofin	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M01CC01	penicillamine	Antiinflammatory and antirheumatic products	Musculo-skeletal system
M02AA01	phenylbutazone	Topical products for joint and muscular pain	Musculo-skeletal system
M02AA07	piroxicam	Topical products for joint and muscular pain	Musculo-skeletal system
M02AA10	ketoprofen	Topical products for joint and muscular pain	Musculo-skeletal system
M02AA12	naproxen	Topical products for joint and muscular pain	Musculo-skeletal system
M02AA13	ibuprofen	Topical products for joint and muscular pain	Musculo-skeletal system
M02AA15	diclofenac	Topical products for joint and muscular pain	Musculo-skeletal system
M02AA23	indometacin = indomethacin	Topical products for joint and muscular pain	Musculo-skeletal system
M03AA02	tubocurarine	Muscle relaxants	Musculo-skeletal system
M03AC02	gallamine	Muscle relaxants	Musculo-skeletal system
M03AC03	vecuronium	Muscle relaxants	Musculo-skeletal system
M03AC04	atracurium	Muscle relaxants	Musculo-skeletal system
M03AC06	pipecuronium = pipecuronium bromide	Muscle relaxants	Musculo-skeletal system
M03AC11	cisatracurium besilate	Muscle relaxants	Musculo-skeletal system
M03AX01	botulinum toxin = incobotulinumtoxin a	Muscle relaxants	Musculo-skeletal system
M03BX01	baclofen	Muscle relaxants	Musculo-skeletal system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
M04AC01	colchicine	Antigout preparations	Musculo-skeletal system
M05BA01	etidronate disodium= etidronic acid	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BA02	clodronate= clodronic acid	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BA03	pamidronate = pamidronic acid	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BA04	alendronate= alendronic acid	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BA06	ibandronic acid = ibandronate	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BA07	risedronate = risedronic acid	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BA08	zoledronic acid	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BC02	eptotermin alfa	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BX03	strontium ranelate	Drugs for treatment of bone diseases	Musculo-skeletal system
M05BX04	denosumab	Drugs for treatment of bone diseases	Musculo-skeletal system
M09AA01	hydroquinine	Other drugs for disorders of the musculo-skeletal system	Musculo-skeletal system
N01AB06	isoflurane	Anesthetics	Nervous system
N01AB07	desflurane	Anesthetics	Nervous system
N01AH01	fentanyl	Anesthetics	Nervous system
N01AH02	alfentanil	Anesthetics	Nervous system
N01AH04	phenoperidine	Anesthetics	Nervous system
N01AH06	remifentanil	Anesthetics	Nervous system
N01AH51	fentanyl and ropivacaine = fentanyl, combinations	Anesthetics	Nervous system
N01AX03	ketamine	Anesthetics	Nervous system
N01AX07	etomidate	Anesthetics	Nervous system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
N01AX10	propofol	Anesthetics	Nervous system
N01BB08	articaine	Anesthetics	Nervous system
N01BB10	levobupivacaine	Anesthetics	Nervous system
N01BB51	bupivacaine and fentanyl	Anesthetics	Nervous system
N01BB58	articaine and adrenaline	Anesthetics	Nervous system
N02AA01	morphine	Analgesics	Nervous system
N02AA03	hydromorphone	Analgesics	Nervous system
N02AA05	oxycodone	Analgesics	Nervous system
N02AA10	papaveretum	Analgesics	Nervous system
N02AA55	oxycodone and naloxone	Analgesics	Nervous system
N02AB02	pethidine	Analgesics	Nervous system
N02AB03	fentanyl	Analgesics	Nervous system
N02AC01	dextromoramide	Analgesics	Nervous system
N02AC04	dextropropoxyphene	Analgesics	Nervous system
N02AD01	pentazocine	Analgesics	Nervous system
N02AE01	buprenorphine	Analgesics	Nervous system
N02AJ13	paracetomol and tramadol	Analgesics	Nervous system
N02AX02	tramadol	Analgesics	Nervous system
N02AX06	tapentadol	Analgesics	Nervous system
N02BA01	aspirin = acetylsalicylic acid	Analgesics	Nervous system
N02BA04	sodium salicylate	Analgesics	Nervous system
N02BA11	diflunisal	Analgesics	Nervous system
N02BG09	methoxyflurane	Analgesics	Nervous system
N02CA01	dihydroergotamine	Analgesics	Nervous system
N02CA02	ergotamine	Analgesics	Nervous system
N02CA04	methysergide	Analgesics	Nervous system
N02CC01	sumatriptan	Analgesics	Nervous system
N02CC02	naratriptan	Analgesics	Nervous system
N02CC03	zolmitriptan	Analgesics	Nervous system
N02CX02	clonidine	Analgesics	Nervous system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
N03AA01	mephobarbital = methylphenobarbital = methylphenobarbitone	Antiepileptics	Nervous system
N03AA02	phenobarbital = phenobarbitone	Antiepileptics	Nervous system
N03AA03	primidone	Antiepileptics	Nervous system
N03AB02	phenytoin	Antiepileptics	Nervous system
N03AB04	mephenytoin	Antiepileptics	Nervous system
N03AC01	paramethadione	Antiepileptics	Nervous system
N03AC02	Trimethadione	Antiepileptics	Nervous system
N03AD01	ethosuximide	Antiepileptics	Nervous system
N03AD02	phensuximide	Antiepileptics	Nervous system
N03AD03	methsuximide = mesuximide	Antiepileptics	Nervous system
N03AE01	clonazepam	Antiepileptics	Nervous system
N03AF01	carbamazepine	Antiepileptics	Nervous system
N03AF02	oxcarbazepine	Antiepileptics	Nervous system
N03AF03	rufinamide	Antiepileptics	Nervous system
N03AG04	vigabatrin	Antiepileptics	Nervous system
N03AG06	tiagabine	Antiepileptics	Nervous system
N03AX03	sultiame	Antiepileptics	Nervous system
N03AX11	topiramate	Antiepileptics	Nervous system
N03AX12	gabapentin	Antiepileptics	Nervous system
N03AX15	zonisamide	Antiepileptics	Nervous system
N03AX16	pregabalin	Antiepileptics	Nervous system
N03AX17	stiripentol	Antiepileptics	Nervous system
N03AX18	lacosamide	Antiepileptics	Nervous system
N03AX21	ezogabine = retigabine	Antiepileptics	Nervous system
N03AX22	perampanel hemisesquihydrate = perampanel	Antiepileptics	Nervous system
N03AX23	brivaracetam	Antiepileptics	Nervous system
N04BA01	levodopa	Anti-parkinson drugs	Nervous system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
N04BA02	benserazide and levodopa = levodopa and decarboxylase inhibitor	Anti-parkinson drugs	Nervous system
N04BA03	carbidopa, entacapone and levodopa	Anti-parkinson drugs	Nervous system
N04BB01	amantadine	Anti-parkinson drugs	Nervous system
N04BC02	pergolide	Anti-parkinson drugs	Nervous system
N04BC04	ropinirole	Anti-parkinson drugs	Nervous system
N04BC05	pramipexole	Anti-parkinson drugs	Nervous system
N04BC07	apomorphine	Anti-parkinson drugs	Nervous system
N04BC09	rotigotine	Anti-parkinson drugs	Nervous system
N04BD02	rasagiline	Anti-parkinson drugs	Nervous system
N04BD03	safinamide mesilate = safinamide	Anti-parkinson drugs	Nervous system
N04BX01	tolcapone	Anti-parkinson drugs	Nervous system
N04BX02	entacapone	Anti-parkinson drugs	Nervous system
N05AA01	chlorpromazine	Psycholeptics	Nervous system
N05AA03	promazine	Psycholeptics	Nervous system
N05AB02	fluphenazine	Psycholeptics	Nervous system
N05AB03	perphenazine	Psycholeptics	Nervous system
N05AB04	prochlorperazine	Psycholeptics	Nervous system
N05AB05	thiopropazate	Psycholeptics	Nervous system
N05AB06	trifluoperazine	Psycholeptics	Nervous system
N05AC01	periciazine	Psycholeptics	Nervous system
N05AC02	thioridazine	Psycholeptics	Nervous system
N05AD01	haloperidol	Psycholeptics	Nervous system
N05AD08	droperidol	Psycholeptics	Nervous system
N05AE03	sertindole	Psycholeptics	Nervous system
N05AE04	ziprasidone	Psycholeptics	Nervous system
N05AF01	flupentixol	Psycholeptics	Nervous system
N05AF04	tiotixene	Psycholeptics	Nervous system
N05AF05	zuclopenthixol	Psycholeptics	Nervous system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
N05AG02	pimozide	Psycholeptics	Nervous system
N05AH01	loxapine	Psycholeptics	Nervous system
N05AH02	clozapine	Psycholeptics	Nervous system
N05AH03	olanzapine	Psycholeptics	Nervous system
N05AH04	quetiapine	Psycholeptics	Nervous system
N05AH05	asenapine	Psycholeptics	Nervous system
N05AL05	amisulpride	Psycholeptics	Nervous system
N05AN01	lithium	Psycholeptics	Nervous system
N05AX08	risperidone	Psycholeptics	Nervous system
N05AX12	aripiprazole	Psycholeptics	Nervous system
N05AX13	paliperidone	Psycholeptics	Nervous system
N05AX16	brexpiprazole	Psycholeptics	Nervous system
N05BA01	diazepam	Psycholeptics	Nervous system
N05BA02	chlordiazepoxide	Psycholeptics	Nervous system
N05BA04	oxazepam	Psycholeptics	Nervous system
N05BA05	clorazepate	Psycholeptics	Nervous system
N05BA06	lorazepam	Psycholeptics	Nervous system
N05BA08	bromazepam	Psycholeptics	Nervous system
N05BA09	clobazam	Psycholeptics	Nervous system
N05BA12	alprazolam	Psycholeptics	Nervous system
N05BC01	meprobamate	Psycholeptics	Nervous system
N05CA01	pentobarbital = pentobarbital = pentobarbitone	Psycholeptics	Nervous system
N05CA02	amobarbital	Psycholeptics	Nervous system
N05CA03	butabarbital	Psycholeptics	Nervous system
N05CA06	secobarbital	Psycholeptics	Nervous system
N05CC05	paraldehyde	Psycholeptics	Nervous system
N05CD01	flurazepam	Psycholeptics	Nervous system
N05CD02	nitrazepam	Psycholeptics	Nervous system
N05CD03	flunitrazepam	Psycholeptics	Nervous system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
N05CD05	triazolam	Psycholeptics	Nervous system
N05CD07	temazepam	Psycholeptics	Nervous system
N05CD08	midazolam	Psycholeptics	Nervous system
N05CF01	zopiclone	Psycholeptics	Nervous system
N05CF02	zolpidem tartrate = zolpidem	Psycholeptics	Nervous system
N05CF03	zaleplon	Psycholeptics	Nervous system
N05CH01	melatonin	Psycholeptics	Nervous system
N06AA01	desipramine	Psychoanaleptics	Nervous system
N06AA02	imipramine	Psychoanaleptics	Nervous system
N06AA04	clomipramine	Psychoanaleptics	Nervous system
N06AA06	trimipramine	Psychoanaleptics	Nervous system
N06AA09	amitriptyline	Psychoanaleptics	Nervous system
N06AA10	nortriptyline	Psychoanaleptics	Nervous system
N06AA11	protriptyline	Psychoanaleptics	Nervous system
N06AA12	doxepin	Psychoanaleptics	Nervous system
N06AA16	dothiepin = dosulepin	Psychoanaleptics	Nervous system
N06AB03	fluoxetine	Psychoanaleptics	Nervous system
N06AB04	citalopram	Psychoanaleptics	Nervous system
N06AB05	paroxetine	Psychoanaleptics	Nervous system
N06AB06	sertraline	Psychoanaleptics	Nervous system
N06AB08	fluvoxamine	Psychoanaleptics	Nervous system
N06AB10	escitalopram	Psychoanaleptics	Nervous system
N06AF03	phenelzine	Psychoanaleptics	Nervous system
N06AG02	moclobemide	Psychoanaleptics	Nervous system
N06AX06	nefazodone	Psychoanaleptics	Nervous system
N06AX11	mirtazapine	Psychoanaleptics	Nervous system
N06AX17	milnacipran	Psychoanaleptics	Nervous system
N06AX21	duloxetine	Psychoanaleptics	Nervous system
N06BA02	dexamfetamine	Psychoanaleptics	Nervous system
N06BA07	modafinil	Psychoanaleptics	Nervous system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
N06BA09	atomoxetine	Psychoanaleptics	Nervous system
N06BA12	lisdexamfetamine dimesilate	Psychoanaleptics	Nervous system
N06BA13	armodafinil	Psychoanaleptics	Nervous system
N06DA01	tacrine	Psychoanaleptics	Nervous system
N06DA02	donepezil	Psychoanaleptics	Nervous system
N07AA02	pyridostigmine	Other nervous system drugs	Nervous system
N07AX01	pilocarpine	Other nervous system drugs	Nervous system
N07BA01	nicotine	Other nervous system drugs	Nervous system
N07BA03	varenicline	Other nervous system drugs	Nervous system
N07BB04	naltrexone	Other nervous system drugs	Nervous system
N07BC02	methadone	Other nervous system drugs	Nervous system
N07XX02	riluzole	Other nervous system drugs	Nervous system
N07XX05	amifampridine	Pher nervous system drugs	Nervous system
N07XX06	tetrabenazine	Other nervous system drugs	Nervous system
N07XX07	fampridine	Other nervous system drugs	Nervous system
P01AB02	tinidazole	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BA01	chloroquine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BA02	hydroxychloroquine	Antiprotozoals	Antiparasitic products, insecticides and repellents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
P01BA03	primaquine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BA07	tafenoquine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BC01	quinine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BC02	mefloquine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BD01	pyrimethamine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BE02	artemether	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01BF01	artemether and lumefantine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01CX01	pentamidine = pentamidine isethionate	Antiprotozoals	Antiparasitic products, insecticides and repellents
P01CX03	eflornithine	Antiprotozoals	Antiparasitic products, insecticides and repellents
P02CA01	mebendazole	Anthelmintics	Antiparasitic products, insecticides and repellents
P02CA02	tiabendazole	Anthelmintics	Antiparasitic products, insecticides and repellents
P02CA03	albendazole	Anthelmintics	Antiparasitic products, insecticides and repellents
P02CE01	levamisole	Anthelmintics	Antiparasitic products, insecticides and repellents

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
P02CF01	ivermectin	Anthelmintics	Antiparasitic products, insecticides and repellents
P03AB02	lindane	Ectoparasiticides, incl. Scabicides	Antiparasitic products, insecticides and repellents
R01AC02	levocabastine	Nasal preparations	Respiratory system
R01AC03	azelastine	Nasal preparations	Respiratory system
R01AD01	beclometasone = beclomethasone	Nasal preparations	Respiratory system
R01AD04	flunisolide	Nasal preparations	Respiratory system
R01AD06	betamethasone valerate = betamethasone acetate	Nasal preparations	Respiratory system
R01AD08	fluticasone propionate = fluticasone	Nasal preparations	Respiratory system
R01AD09	mometasone	Nasal preparations	Respiratory system
R01AD11	triamcinolone	Nasal preparations	Respiratory system
R01AD12	fluticasone furoate	Nasal preparations	Respiratory system
R01AD13	ciclesonide	Nasal preparations	Respiratory system
R01AD58	fluticasone propionate and eformoterol fumarate = fluticasone, combinations	Nasal preparations	Respiratory system
R01AX02	retinol	Nasal preparations	Respiratory system
R01AX08	framycetin	Nasal preparations	Respiratory system
R02AB01	neomycin	Throat preparations	Respiratory system
R03AC12	salmeterol	Drugs for obstructive airway diseases	Respiratory system
R03AC14	Aclidinium bromide / eformoterol fumarate	Drugs for obstructive airway diseases	Respiratory system
R03AC18	indacaterol	Drugs for obstructive airway diseases	Respiratory system
R03AC19	olodaterol hydrochloride = olodaterol	Drugs for obstructive airway diseases	Respiratory system
R03AK06	fluticasone propionate and salmeterol xinafoate = salmeterol and fluticasone	Drugs for obstructive airway diseases	Respiratory system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
R03AK10	fluticasone furoate and vilanterol	Drugs for obstructive airway diseases	Respiratory system
R03AK11	Fluticasone propionate / eformoterol fumarate	Drugs for obstructive airway diseases	Respiratory system
R03AL03	umeclidinium bromide and vilanterol	Drugs for obstructive airway diseases	Respiratory system
R03AL04	indacaterol and glycopyrronium bromide	Drugs for obstructive airway diseases	Respiratory system
R03AL05	eformoterol = formoterol	Drugs for obstructive airway diseases	Respiratory system
R03AL06	olodaterol and tiotropium bromide	Drugs for obstructive airway diseases	Respiratory system
R03AL08	umeclidinium bromide, fluticasone furoate and vilanterol	Drugs for obstructive airway diseases	Respiratory system
R03BA01	beclometasone = beclomethasone	Drugs for obstructive airway diseases	Respiratory system
R03BA03	flunisolide	Drugs for obstructive airway diseases	Respiratory system
R03BA04	betamethasone valerate = betamethasone acetate	Drugs for obstructive airway diseases	Respiratory system
R03BA05	fluticasone propionate	Drugs for obstructive airway diseases	Respiratory system
R03BA06	triamcinolone	Drugs for obstructive airway diseases	Respiratory system
R03BA07	mometasone	Drugs for obstructive airway diseases	Respiratory system
R03BA08	ciclesonide	Drugs for obstructive airway diseases	Respiratory system
R03BA09	fluticasone furoate	Drugs for obstructive airway diseases	Respiratory system
R03BB05	aclidinium bromide	Drugs for obstructive airway diseases	Respiratory system
R06AD01	trimeprazine = alimemazine	Antihistamines for systemic use	Respiratory system
R06AD02	promethazine	Antihistamines for systemic use	Respiratory system

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
R06AD03	thiethylperazine	Antihistamines for systemic use	Respiratory system
R06AE03	cyclizine	Antihistamines for systemic use	Respiratory system
R06AE04	chlorcyclizine	Antihistamines for systemic use	Respiratory system
R06AX19	azelastine	Antihistamines for systemic use	Respiratory system
R07AX02	ivacaftor	Other respiratory system products	Respiratory system
R07AX30	lumacaftor and ivacaftor	Other respiratory system products	Respiratory system
R07AX31	tezacaftor and ivacaftor	Other respiratory system products	Respiratory system
S01AA02	chlortetracycline	Ophthalmologicals	Sensory organs
S01AA03	neomycin	Ophthalmologicals	Sensory organs
S01AA04	oxytetracycline	Ophthalmologicals	Sensory organs
S01AA07	framycetin	Ophthalmologicals	Sensory organs
S01AA09	tetracycline	Ophthalmologicals	Sensory organs
S01AA11	gentamicin	Ophthalmologicals	Sensory organs
S01AA12	tobramycin	Ophthalmologicals	Sensory organs
S01AA13	sodium fusidate = fusidic acid	Ophthalmologicals	Sensory organs
S01AA21	amikacin	Ophthalmologicals	Sensory organs
S01AA23	netilmicin	Ophthalmologicals	Sensory organs
S01AA24	kanamycin	Ophthalmologicals	Sensory organs
S01AB01	sulfamethizole	Ophthalmologicals	Sensory organs
S01AB04	sulfacetamide	Ophthalmologicals	Sensory organs
S01AD01	idoxuridine	Ophthalmologicals	Sensory organs
S01AD03	aciclovir	Ophthalmologicals	Sensory organs
S01AD09	ganciclovir	Ophthalmologicals	Sensory organs
S01AE01	ofloxacin	Ophthalmologicals	Sensory organs
S01AE02	norfloxacin	Ophthalmologicals	Sensory organs

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
S01AE03	ciprofloxacin	Ophthalmologicals	Sensory organs
S01AE04	lomefloxacin	Ophthalmologicals	Sensory organs
S01AE05	levofloxacin	Ophthalmologicals	Sensory organs
S01AE06	gatifloxacin	Ophthalmologicals	Sensory organs
S01AE07	moxifloxacin	Ophthalmologicals	Sensory organs
S01BA06	betamethasone valerate = betamethasone acetate	Ophthalmologicals	Sensory organs
S01BA07	fluorometholone	Ophthalmologicals	Sensory organs
S01BA11	Desonide	Ophthalmologicals	Sensory organs
S01BC03	diclofenac	Ophthalmologicals	Sensory organs
S01BC05	ketorolac	Ophthalmologicals	Sensory organs
S01BC06	piroxicam	Ophthalmologicals	Sensory organs
S01BC10	nepafenac	Ophthalmologicals	Sensory organs
S01CB04	betamethasone valerate = betamethasone acetate	Ophthalmologicals	Sensory organs
S01CB05	fluorometholone	Ophthalmologicals	Sensory organs
S01EA03	apraclonidine	Ophthalmologicals	Sensory organs
S01EA04	clonidine	Ophthalmologicals	Sensory organs
S01EA05	brimonidine tartrate	Ophthalmologicals	Sensory organs
S01EB01	pilocarpine	Ophthalmologicals	Sensory organs
S01EB05	physostigmine	Ophthalmologicals	Sensory organs
S01EC01	acetazolamide	Ophthalmologicals	Sensory organs
S01EC03	dorzolamide	Ophthalmologicals	Sensory organs
S01EC04	brinzolamide	Ophthalmologicals	Sensory organs
S01EC54	brimonidine and brinzolamide = brinzolamide, combinations	Ophthalmologicals	Sensory organs
S01ED01	timolol	Ophthalmologicals	Sensory organs
S01ED02	betaxolol	Ophthalmologicals	Sensory organs
S01ED03	levobunolol	Ophthalmologicals	Sensory organs
S01ED51	bimatoprost and timolol = timolol, combinations	Ophthalmologicals	Sensory organs

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
S01EE01	latanoprost	Ophthalmologicals	Sensory organs
S01EE02	unoprostone isopropyl (unoprostone)	Ophthalmologicals	Sensory organs
S01EE03	bimatoprost	Ophthalmologicals	Sensory organs
S01EE04	travoprost	Ophthalmologicals	Sensory organs
S01EE05	tafluprost	Ophthalmologicals	Sensory organs
S01GX02	levocabastine	Ophthalmologicals	Sensory organs
S01GX07	azelastine	Ophthalmologicals	Sensory organs
S01HA02	oxybuprocaine	Ophthalmologicals	Sensory organs
S01LA01	verteporfin	Ophthalmologicals	Sensory organs
S01LA04	ranibizumab	Ophthalmologicals	Sensory organs
S01LA05	aflibercept	Ophthalmologicals	Sensory organs
S01XA02	retinol	Ophthalmologicals	Sensory organs
S01XA14	heparin	Ophthalmologicals	Sensory organs
S01XA18	ciclosporin	Ophthalmologicals	Sensory organs
S01XA21	cysteamine bitartrate = mercaptamine bitartrate	Ophthalmologicals	Sensory organs
S01XA23	sirolimus	Ophthalmologicals	Sensory organs
S02AA07	neomycin	Otologicals	Sensory organs
S02AA08	tetracycline	Otologicals	Sensory organs
S02AA14	gentamicin	Otologicals	Sensory organs
S02AA15	ciprofloxacin	Otologicals	Sensory organs
S02AA16	ofloxacin	Otologicals	Sensory organs
S02BA07	betamethasone valerate = betamethasone acetate	Otologicals	Sensory organs
S03AA01	neomycin	Ophthalmological and otological preparations	Sensory organs
S03AA02	tetracycline	Ophthalmological and otological preparations	Sensory organs
S03AA06	gentamicin	Ophthalmological and otological preparations	Sensory organs
S03AA07	ciprofloxacin	Ophthalmological and otological preparations	Sensory organs

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
S03BA03	betamethasone valerate = betamethasone acetate	Ophthalmological and otological preparations	Sensory organs
V03AB17	methylene blue = methylthioninium chloride	Antidotes	Various
V03AB19	physostigmine	Antidotes	Various
V03AB25	flumazenil	Antidotes	Various
V03AC01	deferoxamine	Iron chelating agents	Various
V03AC02	deferiprone	Iron chelating agents	Various
V03AC03	deferasirox	Iron chelating agents	Various
V03AE02	sevelamer	Drugs for treatment of hyperkalemia and hyperphosphatemia	Various
V03AE03	lanthanum carbonate	Drugs for treatment of hyperkalemia and hyperphosphatemia	Various
V03AE05	sucroferric oxyhydroxide	Drugs for treatment of hyperkalemia and hyperphosphatemia	Various
V03AF05	amifostine	Detoxifying agents for antineoplastic treatment	Various
V03AF08	palifermin	Detoxifying agents for antineoplastic treatment	Various
V03AH01	diazoxide	Drugs for treatment of hypoglycemia	Various
V04CA01	tolbutamide	Diagnostic agents	Various
V04CX05	13C-urea	Diagnostic agents	Various
V08AB10	iomeprol	Contrast media	Various
V08CA03	gadodiamide	Contrast media	Various
V08CA04	gadoteridol	Contrast media	Various
V08CA06	gadoversetamide	Contrast media	Various
V08CA08	gadobenate = gadobenic acid	Contrast media	Various
V08CA09	gadobutrol	Contrast media	Various
V08CA10	gadoxetate = gadoxetic acid	Contrast media	Various
V08CA11	gadofosveset	Contrast media	Various

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
V08DA01	perflutren = perflutren, human albumin microspheres	Contrast media	Various
V08DA04	perflutren = perflutren, phospholipid microspheres	Contrast media	Various
V09AA01	technetium (99mTc) exametazime	Diagnostic radiopharmaceuticals	Various
V09AA02	technetium (99mTc) bicisate	Diagnostic radiopharmaceuticals	Various
V09AB01	iodine iofetamine (123I)	Diagnostic Radiopharmaceuticals	Various
V09AB02	iodine iolopride (123I)	Diagnostic Radiopharmaceuticals	Various
V09AB03	iodine iofluphane (123I)	Diagnostic Radiopharmaceuticals	Various
V09BA01	technetium (99mTc) oxidronic acid	Diagnostic radiopharmaceuticals	Various
V09BA02	technetium (99mTc) medronic acid	Diagnostic radiopharmaceuticals	Various
V09BA03	technetium (99mTc) pyrophosphate	Diagnostic radiopharmaceuticals	Various
V09BA04	technetium (99mTc) butedronic acid	Diagnostic radiopharmaceuticals	Various
V09CA01	technetium (99mTc) pentetic acid	Diagnostic radiopharmaceuticals	Various
V09CA02	technetium (99mTc) succimer	Diagnostic radiopharmaceuticals	Various
V09CA03	technetium (99mTc) mertiatide	Diagnostic radiopharmaceuticals	Various
V09CA04	technetium (99mTc) gluceptate	Diagnostic radiopharmaceuticals	Various
V09CA05	technetium (99mTc) gluconate	Diagnostic radiopharmaceuticals	Various
V09CA06	technetium (99mTc) ethylenedicysteine	Diagnostic radiopharmaceuticals	Various
V09DA01	technetium (99mTc) disofenin	Diagnostic radiopharmaceuticals	Various

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
V09DA02	technetium (99mTc) etifenin	Diagnostic radiopharmaceuticals	Various
V09DA03	technetium (99mTc) lidofenin	Diagnostic radiopharmaceuticals	Various
V09DA04	technetium (99mTc) mebrofenin	Diagnostic radiopharmaceuticals	Various
V09DA05	technetium (99mTc) galtifenin	Diagnostic radiopharmaceuticals	Various
V09DB01	technetium (99mTc) nanocolloid	Diagnostic radiopharmaceuticals	Various
V09DB02	technetium (99mTc) microcolloid	Diagnostic radiopharmaceuticals	Various
V09DB03	technetium (99mTc) millimicrospheres	Diagnostic radiopharmaceuticals	Various
V09DB04	technetium (99mTc) tin colloid	Diagnostic radiopharmaceuticals	Various
V09DB05	technetium (99mTc) sulfur colloid	Diagnostic radiopharmaceuticals	Various
V09DB06	technetium (99mTc) rheniumsulfide colloid	Diagnostic radiopharmaceuticals	Various
V09DB07	technetium (99mTc) phytate	Diagnostic radiopharmaceuticals	Various
V09EA01	technetium (99mTc) pentetic acid	Diagnostic radiopharmaceuticals	Various
V09EA02	technetium (99mTc) technegas	Diagnostic radiopharmaceuticals	Various
V09EA03	technetium (99mTc) nanocolloid	Diagnostic radiopharmaceuticals	Various
V09EB01	technetium (99mTc) macrosalb	Diagnostic radiopharmaceuticals	Various
V09EB02	technetium (99mTc) microspheres	Diagnostic radiopharmaceuticals	Various
V09FX02	sodium iodide (123I)	Therapeutic radiopharmaceuticals	Various
V09FX03	sodium iodide (131I)	Therapeutic radiopharmaceuticals	Various

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
V09FX04	sodium iodide (124I)	Therapeutic radiopharmaceuticals	Various
V09GA01	technetium (99mTc) sestamibi	Diagnostic radiopharmaceuticals	Various
V09GA02	technetium (99mTc) tetrofosmin	Diagnostic radiopharmaceuticals	Various
V09GA03	technetium (99mTc) teboroxime	Diagnostic radiopharmaceuticals	Various
V09GA04	technetium (99mTc) human albumin	Diagnostic radiopharmaceuticals	Various
V09GA05	technetium (99mTc) furifosmin	Diagnostic radiopharmaceuticals	Various
V09GA06	technetium (99mTc) stannous agent labelled cells	Diagnostic radiopharmaceuticals	Various
V09GA07	technetium (99mTc) apcitide	Diagnostic radiopharmaceuticals	Various
V09GB01	fibrinogen (125I)	Diagnostic Radiopharmaceuticals	Various
V09GB02	iodine (125I) human albumin	Diagnostic Radiopharmaceuticals	Various
V09HA01	technetium (99mTc) human immunoglobulin	Diagnostic radiopharmaceuticals	Various
V09HA02	technetium (99mTc) exametazime labelled cells	Diagnostic radiopharmaceuticals	Various
V09HA03	technetium (99mTc) antigranulocyte antibody	Diagnostic radiopharmaceuticals	Various
V09HA04	technetium (99mTc) sulesomab	Diagnostic radiopharmaceuticals	Various
V09IA01	technetium (99mTc) antiCarcinoEmbryonicAntigen antibody	Diagnostic radiopharmaceuticals	Various
V09IA02	technetium (99mTc) antimelanoma antibody	Diagnostic radiopharmaceuticals	Various
V09IA03	technetium (99mTc) pentavalent succimer	Diagnostic radiopharmaceuticals	Various

ATC code	Name (5th level ATC, chemical substance)	2nd level ATC, therapeutic subgroup	1st level ATC, anatomical main group
V09IA04	technetium (99mTc) votumumab	Diagnostic radiopharmaceuticals	Various
V09IA05	technetium (99mTc) depreotide	Diagnostic radiopharmaceuticals	Various
V09IA06	technetium (99mTc) arcitumomab	Diagnostic radiopharmaceuticals	Various
V09IA07	technetium (99mTc) hynic-octreotide	Diagnostic radiopharmaceuticals	Various
V09IA08	technetium (99mTc) etarfolatide	Diagnostic radiopharmaceuticals	Various
V09IA09	technetium (99mTc) tilmanocept	Diagnostic radiopharmaceuticals	Various
V09XA01	iodine (131I) norcholesterol	Diagnostic radiopharmaceuticals	Various
V09XA02	iodocholesterol (131I)	Diagnostic radiopharmaceuticals	Various
V09XA03	iodine (131I) human albumin	Diagnostic radiopharmaceuticals	Various
V10AX02	samarium [153sm] = samarium (153Sm) hydroxyapatite colloid	Therapeutic radiopharmaceuticals	Various
V10XA01	sodium iodide (131I)	Therapeutic radiopharmaceuticals	Various
V10XA03	tositumomabandiodine (131I) tositumomab	Therapeutic radiopharmaceuticals	Various
V10XX01	sodium phosphate [32p]	Therapeutic radiopharmaceuticals	Various
V10XX03	radium (223Ra) dichloride	Therapeutic radiopharmaceuticals	Various

ATC: Anatomical Therapeutic Chemical

Table 57: AEDs excluding the study drugs

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AA01	Methylphenobarbital	Barbiturates and derivatives
N03AA02	Phenobarbital	Barbiturates and derivatives

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AA03	Primidone	Barbiturates and derivatives
N03AA04	Barbexaclone	Barbiturates and derivatives
N03AA30	Metharbital	Barbiturates and derivatives
N03AB01	Ethotoin	Hydantoin derivatives
N03AB02	Phenytoin	Hydantoin derivatives
N03AB03	Amino(diphenylhydantoin) valeric acid	Hydantoin derivatives
N03AB04	Mephenytoin	Hydantoin derivatives
N03AB05	Fosphenytoin	Hydantoin derivatives
N03AB52	Phenytoin, combinations	Hydantoin derivatives
N03AB54	Mephenytoin, combinations	Hydantoin derivatives
N03AC01	Paramethadione	Oxazolidine derivatives
N03AC02	Trimethadione	Oxazolidine derivatives
N03AC03	Ethadione	Oxazolidine derivatives
N03AD01	Ethosuximide	Succinimide derivatives
N03AD02	Phensuximide	Succinimide derivatives
N03AD03	Mesuximide	Succinimide derivatives
N03AD51	Ethosuximide, combinations	Succinimide derivatives
N03AE01	Clonazepam	Benzodiazepine derivatives
N03AF01	Carbamazepine	Carboxamide derivatives
N03AF02	Oxcarbazepine	Carboxamide derivatives
N03AF03	Rufinamide	Carboxamide derivatives
N03AF04	Eslicarbazepine	Carboxamide derivatives
N03AG03	Aminobutyric acid	Fatty Acid derivatives
N03AG04	Vigabatrin	Fatty Acid derivatives
N03AG05	Progabide	Fatty Acid derivatives
N03AG06	Tiagabine	Fatty Acid derivatives
N03AX03	Sultiame	Other Antiepileptics
N03AX07	Phenacemide	Other Antiepileptics
N03AX10	Felbamate	Other Antiepileptics
N03AX11	Topiramate	Other Antiepileptics
N03AX12	Gabapentin	Other Antiepileptics
N03AX13	Pheneturide	Other Antiepileptics

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AX15	Zonisamide	Other Antiepileptics
N03AX16	Pregabalin	Other Antiepileptics
N03AX17	Stiripentol	Other Antiepileptics
N03AX18	Lacosamide	Other Antiepileptics
N03AX19	Carisbamate	Other Antiepileptics
N03AX21	Retigabine	Other Antiepileptics
N03AX22	Perampanel	Other Antiepileptics
N03AX23	Brivaracetam	Other Antiepileptics
N03AX24	Cannabidiol	Other Antiepileptics
N03AX30	Beclamide	Other Antiepileptics

ATC: Anatomical Therapeutic Chemical

Table 58: AEDs all

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AA01	methylphenobarbital	Barbiturates and derivatives
N03AA02	phenobarbital	Barbiturates and derivatives
N03AA03	primidone	Barbiturates and derivatives
N03AA04	barbexaclone	Barbiturates and derivatives
N03AA30	metharbital	Barbiturates and derivatives
N03AB01	ethotoin	Hydantoin derivatives
N03AB02	phenytoin	Hydantoin derivatives
N03AB03	amino(diphenylhydantoin) valeric acid	Hydantoin derivatives
N03AB04	mephenytoin	Hydantoin derivatives
N03AB05	fosphenytoin	Hydantoin derivatives
N03AB52	phenytoin, combinations	Hydantoin derivatives
N03AB54	mephenytoin, combinations	Hydantoin derivatives
N03AC01	paramethadione	Oxazolidine derivatives
N03AC02	trimethadione	Oxazolidine derivatives
N03AC03	ethadione	Oxazolidine derivatives
N03AD01	ethosuximide	Succinimide derivatives
N03AD02	phensuximide	Succinimide derivatives
N03AD03	mesuximide	Succinimide derivatives
N03AD51	ethosuximide, combinations	Succinimide derivatives
N03AE01	clonazepam	Benzodiazepine derivatives
N03AF01	carbamazepine	Carboxamide derivatives
N03AF02	oxcarbazepine	Carboxamide derivatives
N03AF03	rufinamide	Carboxamide derivatives
N03AF04	eslicarbazepine	Carboxamide derivatives
N03AG01	valproic acid *	Fatty Acid derivatives
N03AG02	valpromide *	Fatty Acid derivatives
N03AG03	aminobutyric acid	Fatty Acid derivatives
N03AG04	vigabatrin	Fatty Acid derivatives
N03AG05	progabide	Fatty Acid derivatives
N03AG06	tiagabine	Fatty Acid derivatives
N03AX03	sultiame	Other Antiepileptics
N03AX07	phenacemide	Other Antiepileptics
N03AX09	lamotrigine *	Other Antiepileptics

ATC code	Name (5th level ATC, chemical substance)	4th level ATC, chemical subgroup
N03AX10	felbamate	Other Antiepileptics
N03AX11	topiramate	Other Antiepileptics
N03AX12	gabapentin	Other Antiepileptics
N03AX13	pheneturide	Other Antiepileptics
N03AX14	levetiracetam *	Other Antiepileptics
N03AX15	zonisamide	Other Antiepileptics
N03AX16	pregabalin	Other Antiepileptics
N03AX17	stiripentol	Other Antiepileptics
N03AX18	lacosamide	Other Antiepileptics
N03AX19	carisbamate	Other Antiepileptics
N03AX21	retigabine	Other Antiepileptics
N03AX22	perampanel	Other Antiepileptics
N03AX23	brivaracetam	Other Antiepileptics
N03AX24	cannabidiol	Other Antiepileptics
N03AX30	beclamide	Other Antiepileptics

AED: Anti-Epileptic Drug, ATC: Anatomical Therapeutic Chemical
* Study drugs

Table 59: Offspring drug syndrome

ICD 10	Clinical Code Description
P044	Foetus and newborn affected by maternal use of drugs of addiction
P961	Neonatal withdrawal symptom from maternal use of drug of addiction

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 60: Offspring diabetes

ICD 10	Clinical Code Description
P701	Syndrome of infant of a diabetic mother

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

Table 61: Offspring gestational diabetes

ICD 10	Clinical Code Description
P700	Syndrome of infant of mother with gestational diabetes

ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision.

ANNEX 4. MARKETING AUTHORISATION HOLDERS (MAHS) DETAILS

Table 62: List of Marketing Authorisation Holders (MAHs)

MAH	Name	Email
APOTEX EUROPE B.V.	Marjolein Los	PharmacovigilanceBNL@aurobindo.com
APOTEX EUROPE B.V.	JHENGSTUM	JHENGSTUM@aurobindo.com
APOTEX EUROPE B.V.	Rex Alexander	rex.alexander@aurobindo.com
Aristo Pharma GMBH	Farah Khaznadar	Farah.Khaznadar@aristo-pharma.de
Aristo Pharma GMBH		pharmacovigilance@aristo-pharma.de
Aristo Pharma GMBH	Danny Bartholome	Danny.Bartholome@aristo-pharma.de
Aristo Pharma GMBH		QPPV-Office-Aristo@pharmalex.com
Arrow Generiques	Sandrine Paitreault	Spaitreault@arrow-generiques.com
Arrow Generiques	Sophie Seguin	sseguin@laboratoire-arrow.com
Arrow Generiques		PharmacovigilanceFR@laboratoire-arrow.com
Arrow Generiques	Marine Lemoine	mlemoine@laboratoire-arrow.com
Betapharma Arzneimittel GMBH	Monika Haidinger	Monika.haidinger@drreddys.com
Betapharma Arzneimittel GMBH	Anika Staack	anika.staack@drreddys.com
CONSILIENT HEALTH LTD	Tony Fakhouri	tfakhouri@consilienthealth.com
CONSILIENT HEALTH LTD	Helena Hellmerichs	hhellmerichs@consilienthealth.com
CONSILIENT HEALTH LTD	Tamara Kokaz	tkokaz@consilienthealth.com
CONSILIENT HEALTH LTD	Nawal Mahfoudh Jebbar	nawalmahfoudh.jebbar@propharmagroup.com
CONSILIENT HEALTH LTD		drugsafety@consilienthealth.com
CONSILIENT HEALTH LTD	Jason Connell	JConnell@diamondpharmaservices.com
CONSILIENT HEALTH LTD	George Forrester	GForrester@diamondpharmaservices.com
CONSILIENT HEALTH LTD	Nikhil Kamble	RA@consilienthealth.com
CRESCENT PHARMA LTD	Gordon Shearer	GShearer@crescentpharma.com
CRESCENT PHARMA LTD	Samie Aldoori	SAldoori@crescentpharma.com
CRESCENT PHARMA LTD	Akshay Dhavalikar	adhavalikar@crescentpharma.com
CRESCENT PHARMA LTD	Amirah Panwar	Amirah.Panhwar@apcerls.com
CRESCENT PHARMA LTD		Rajasekhar.Ranabothu@apcerls.com
DESITIN ARZNEIMITTEL GMBH	Franziska Kuehn	kuehn@desitin.de
DESITIN ARZNEIMITTEL GMBH	Corinna Hansen	hansen@desitin.de
DESITIN ARZNEIMITTEL GMBH	Birte Jans	jans@desitin.de
Generis Pharmaceutica	Rita Maduro	rmaduro@aurobindo.com
Generis Pharmaceutica		Pharmacovigilance.Portugal@aurobindo.com
G.L. PHARMA GMBH	Ilse Bartenstein	ilse.bartenstein@gl-pharma.at
G.L. PHARMA GMBH	Christof Wachter	Christof.Wachter@gl-pharma.at
G.L. PHARMA GMBH	Claudia Ulrich	claudia.ulrich@gl-pharma.at
G.L. PHARMA GMBH	Ingrid Kratzer	Ingrid.Kratzer@gl-pharma.at
Hexal AG	Stella Boehmert	stella.boehmert@sandoz.com;
LUPIN HEALTHCARE (UK) LTD,	Ben Ellis	benellis@lupin.com

MAH	Name	Email
LUPIN HEALTHCARE (UK) LTD,	Nicole Dietrich	nicoledietrich@lupin.com
LUPIN HEALTHCARE (UK) LTD,	Olga Heidrich	olgaheidrich@hormosan.de
LUPIN HEALTHCARE (UK) LTD,	Dr Monika Boos	monikaboos@hormosan.de
LUPIN HEALTHCARE (UK) LTD,	Katy Pilling	katypilling@lupin.com
NEURAXPHARM ARZNEIMITTEL GMBH	Christine Pfankuch	c.pfankuch@neuraxpharm.de
NEURAXPHARM ARZNEIMITTEL GMBH	Ilona Schonn	ilona.schonn@elbpv.de
NEURAXPHARM ARZNEIMITTEL GMBH	Fernanda Pulido	fpulido@neuraxpharm.com
Orion corporation	Jukka Pesonen	jukka.pesonen@orionpharma.com
Orion corporation		reshma.karekar@orion.fi
Orion corporation		antti.miettinen@orionpharma.com
Orion corporation	Svetlana Novikova	svetlana.novikova@orionpharma.com
SANOFI AVENTIS GROUPE	Michele Martin	Michele.Martin@sanofi.com
SANOFI AVENTIS GROUPE	Sandrine Leroy	Sandrine.Leroy@sanofi.com
SANOFI AVENTIS GROUPE	Denis Granados	Denis.Granados@sanofi.com
SANOFI AVENTIS GROUPE	Sara Villeneuve	Sara.Villeneuve-ext@sanofi.com
SANOFI AVENTIS GROUPE	Juliette Longin	Juliette.Longin-ext@sanofi.com
SANOFI AVENTIS GROUPE	Sandrine Colas	sandrine.colas@sanofi.com
STADA ARZNEIMITTEL AG		dso@stada.de
STADA ARZNEIMITTEL AG	Justyna Christ	justyna.christ@stada.de
TECNIFAR S.A.	Antonio Costa	Antonio.costa@tecnifar.pt
TECNIFAR S.A.		cecilia.pinto@tecnifar.pt
TECNIFAR S.A.		Irene.Rocha@tecnifar.pt
TECNIFAR S.A.		Telma.Costa@tecnifar.pt
TECNIFAR S.A.		Farmalerta@tecnifar.pt
TECNIFAR S.A.	Sara Costa	sara.costa@zemirpharma.com
TEVA PHARMACEUTICALS EUROPE B.V.	Isabelle George	Isabelle.George@tevafrance.com
TEVA PHARMACEUTICALS EUROPE B.V.	Sigalit Kaplan	sigalit.Kaplan@teva.co.il
VIATRIS HEALTHCARE SAS (FORMERLY MYLAN EMEA SAS)	Balwant Heer	balwant.heer@viatris.com
VIATRIS HEALTHCARE SAS (FORMERLY MYLAN EMEA SAS)		PV.SSTNIS@viatris.com
VIATRIS HEALTHCARE SAS (FORMERLY MYLAN EMEA SAS)	Prashanth Yamparala	prashanth.yamparala@viatris.com
VIATRIS HEALTHCARE SAS (FORMERLY MYLAN EMEA SAS)	Venubabu Garlapati	Venubabu.Garlapati@viatris.com
VIATRIS HEALTHCARE SAS (FORMERLY MYLAN EMEA SAS)	Eiko Soehlke	eiko.soehlke@viatris.com
WOCKHARDT UK LIMITED	Andrew Russell	Andrew.Russell@Wockhardt.co.uk
WOCKHARDT UK LIMITED	Amit Kumar	Amit.Kumar@wockhardt.co.uk