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Study Protocol

Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends

Version 1.1

03 December 2021

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1. TITLE

Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends (EU PAS Register number: 31001).

2. MARKETING AUTHORISATION HOLDER

Not applicable

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4. ABSTRACT

Title

"Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends" (EU PAS Register number: 31001).

Version 1.1 – 03 December 2021, Main authors: Dr Romin Pajouheshnia, Utrecht University, Utrecht, The Netherlands; Prof. Olaf Klungel, Utrecht University, Utrecht, The Netherlands.

Rationale and background

Valproates are licensed for the treatment of epilepsy and manic episodes in patients with bipolar disorder in Europe, in some EU Member States also for the prophylaxis of migraine. Due to an identified risk of malformations and neurodevelopmental disorders of children exposed in utero, valproate and related substances should be avoided for women of childbearing potential. In 2018, a pregnancy prevention programme (PPP) was implemented, as required by the PRAC, to prevent valproate exposure during pregnancy.

The study plan has been developed under the Framework service contract (nr. EMA/2017/09/PE/04) with regard to the re-opening of competition no.2. The objective of this protocol is to describe a study to investigate the use of valproate-containing medicinal products authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice.

Research question and objectives

This study will address the research question, "What was the effect of the EU label changes and the revised pregnancy prevention programme (2018) on utilization of valproate containing medicinal products and to what extent did prescribers and patients comply with recommendations?". To answer this we will complete the following objectives:

Objective 1. To determine drug utilisation and prescription patterns of medicinal products containing valproate and related substances in females of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred.

Objective 2. To determine prescribers' compliance with recommendations included in sections 4.2, 4.3, 4.4 and 4.6 of the SmPC for medicinal products containing valproate and related substances.

Objective 3. To determine, in so far as is possible, patients' use of effective contraception in compliance with sections 4.4 and 4.6 of the SmPC for medicinal products containing valproate and related substances.

Objective 4. To determine drug utilisation and prescription patterns over time for alternative medicines (with particular focus on the whole class of antiepileptic medicines) prescribed in females of childbearing potential or female becoming pregnant where medicinal products containing valproate and related substances had previously been prescribed or discontinued.

Objective 5. Based on the results of above objectives, to estimate the effectiveness of the 2018 risk minimisation measures.

Study design The study design for the different objectives will be a time series study, where outcomes (drug utilization, pregnancy prevention measures, pregnancy) are assessed every month. The study period will run from January 1st, 2010 – December 21st, 2020.

Population Female subjects of childbearing potential (age 12-55 years)

Variables

All Objectives: Exposure to valproate-containing medicinal products: valproic acid, sodium valproate, magnesium valproate, valproate semisodium and valpromide; duration of time on therapy; age; country; indication for valproate use (epilepsy, bipolar disorder and migraine prophylaxis).

Objective 1: Use and discontinuation of valproates, reason for valproate discontinuation

Objectives 2: Pregnancy testing, contraceptive measures, procedures causing infertility

Objective 3: Pregnancy: date of conception, pregnancy outcome

Objective 4: Exposure and switching to alternative medicines

Data sources The study will be performed in the following databases: PHARMO (Netherlands), CPRD (United Kingdom), Danish National Registries, ARS (Italy), BIFAP (Spain).

Study size Approximately 8 million women of childbearing age. Study period: Jan 1 2010 – Dec 31 2020.

Data analysis

Objective 1: Descriptive and hypothesis testing. Monthly period prevalence estimates (MPP), monthly incidence of valproate use, stratified by indication, incident/prevalent user, age group, dose, duration and country. MPPs of discontinuers, estimated as the number of discontinuers divided by the number of users in the prior quarter, stratified by indication, age group, dose, reason for discontinuation. Interrupted time series analysis (ITS) to test an overall change in valproate prescription post-intervention.

Objective 2: Descriptive and hypothesis testing. Proportions of valproate treatment episodes with physician-confirmed pregnancy test at the start of and during an episode, stratified by country, indication, age group, duration of use and dose of valproate. ITS analysis to test for a change in pregnancy testing (prior to the start of an episode and during an episode) before and after the intervention. Proportion of valproate prescriptions/dispensing falling within an episode of contraception use, per month, stratified by country, indication, age group, duration, method of contraception and dose of valproate. ITS analysis to test for a change in frequency of prescriptions during contraception before and after the intervention.

Objective 3: Descriptive and hypothesis testing. Monthly incidence rates of pregnancy during valproate treatment episodes, stratified by country, age-group and indication. ITS analysis to test for a change in incidence of pregnancies during valproate exposure per six months after the intervention.

Objective 4: Descriptive and hypothesis testing. MPP of treatment switchers estimated as the number of women who switched to an alternative medication divided by the total number of valproate users in the prior month. ITS analyses to test for a change in frequency of switching alternative medications after the intervention.

Objective 5: Overall evaluation. Integration of descriptive and ITS analyses from objectives 1-4 to draw conclusions on the effectiveness of the 2018 risk minimization measures.

Milestones
Final study report will be available in December 2021.

5. AMENDMENTS AND UPDATES

Date	Amendment	Justification	Protocol Section
19 May 2020	Inclusion of co-investogators: Ms. Hoxhaj, Dr. Brøgger Kristiansen, Drs. Penning-van Beest	Ms. Hoxhaj will develop data quality checks; Dr. Brøgger Kristiansen will act as data manager for Uni. Copenhagen; Dr. Penning-van Beest took over role of Dr. Houben during planned absence.	3. Responsible parties
	Interim analysis will be conducted in November 2020 (internal milestone)	Interim analysis timelines pushed back due to data access delays following COVID-19 pandemic	6. Deliverables and Milestones
	Pregnancy testing for PHARMO now indicated as "not available". PHARMO will extract any available data on pregnancy tests, but in the likely event that the coverage is too poor, PHARMO will not contribute to pregnancy testing analyses.	On review, a decision was made that PHARMO will likely not have enough pregnancy testing data (as it is mostly OTC) to contribute to the analysis. This will be acknowledged as a limitation.	9. Research methods Table 1 9.9. Limitations of the research methods
03 December 2021	Changes in the study investigators	This accounts for changes in the team structures over the study period.	3. Responsible parties
	Minor changes to internal timelines (no changes to deliverable timelines)	More time was needed to run the interim quality checks (level 1 checks) and complete the ETL, due to the time required to run the quality checks and due to unexpected delays in access to data for some data sources.	6. Deliverables and milestones
	Study design text corrected	The study design text was previously, erroneously described as a longitudinal cohort, when in fact the analyses were for a time-series design (repeated cross-sections over a period of time).	9.1 Study Design 4. Abstract

	Inclusion of the phrase, "having at least one year of valid data" in the study design description	This detail was missing in the first protocol, but is essential to define the study population with the available data	9.2 Setting
	Clarified description of how treatment duration will be estimated	The previous description was imprecise and not sufficiently specific. We now provide a more precise description of how the length of an individual prescription or dispensing will be estimated across data sources.	9.3.1 Exposure definition
	Pregnancy algorithm	It was originally proposed that pregnancies would be identified in all data sources using the Matcho algorithm. Two changes are proposed: 1) Data sources are now flexible to use registry data, if available, to define pregnancies together with or instead of diagnostic codes, if they believe this will be more accurate (PHARMO, CPRD, ARS); 2) the Matcho algorithm has since been extended by members of this consortium by integrating the existing pregnancy algorithm for the BIFAP data source.	9.3.2 – outcomes
	Change in data availability – Danish National Registers can only provide prescribing information until 2018;	Due to severe delays in access to the Danish data source, as a result of prioritization of COVID-19-related projects by the data holder, only a portion of the expected Danish National Register data will be available by the study end date. A readily available data set, including only prescribing data up until the end of 2018 will be used for objectives 1,2,4. As a result, neither objective 3 (pregnancy), nor the analyses stratified by diagnostic information (indication, reason for discontinuation) can be reported on within the study period. A more extensive description of this has been provided to the EMA. We describe this limitation now in section 9.9	9.4.2 Data availability 9.9 Limitations
	Change in data availability for ARS Toscana	It was found that pregnancy testing is insufficiently well-captured in the ARS Toscana data source to be used in this study (as pregnancy tests are not	9.4.2 Data availability

		reimbursed).	
	Monthly instead for quarterly analysis. (In text QPP is changed to MPP for period prevalences)	This is motivated by two factors: 1) Due to COVID-19, the validity of time series data after February 2020 is debatable. Therefore, we need to maximize the number of time points before this, after implementation of the PPP in order to run the ITS analysis 2) Not all data sources can provide data up to 2020 (for example end of 2018 or end of 2019). Therefore, monthly intervals help to maximize the number of time points after the PPP for the ITS analysis.	9.7 Data analysis 4. Abstract
	Segmented regression methodology corrected	Due to the limited post-intervention period in some data sources and analyses, and due to the variable implementation length of implementation period across data sources, a 2-segmented regression analysis is proposed, as it will have more power to detect change due to the PPP. Second, the exact start months of the PPP in each country will be used as the intervention date, instead of July 2018, as this is more accurate. Therefore this will be the primary analysis.	9.4 PRAC Intervention 9.7 Data analysis
	Inclusion of additional sensitivity analysis to exclude COVID-19 pandemic period from analyses	The COVID-19 pandemic may influence the rates of prescribing, and other study outcomes, violating the assumptions of the ITS analysis. Therefore, sensitivity analyses will be conducted to examine the effect of excluding this period of time form each ITS analysis. We describe this as a limitation now in section 9.9	9.7 Data analysis 9.9 Limitations
	Common data model tables updated	The final analysis will use the latest version of the ConcePTION CDM (v2.2). The full tables are available in a link provided in the Appendix	Annex 3
	Text correction from women to females	The description of study subjects is changed from "women" to "female subjects" to recognize that minors under the age of 18 are included in the study.	All sections.

	Minor typographical corrections	Minor typos (such as repeated words), where detected, have been corrected. In some sections of text (e.g. Section 8) text has been slightly reworded to make it less ambiguous.	For example: 4. Abstract, 8 research question and objectives
	Delete limitation: "At the planned analysis stage, BIFAP will only be able to provide data through 31 December 2019. This will impact our ability to conduct ITS in BIFAP alone and to draw conclusions in database-stratified analyses regarding BIFAP. However, data provided by BIFAP in the post-intervention period through 31 December 2019 will contribute to pooled ITS analyses for all time points through the end of 2019."	The AEMPS team has confirmed data availability until 2021 Q2-3	Section 9.9

6. DELIVERABLES AND MILESTONES

Deliverables

Deliverable	Date
Preliminary study plan	25th April 2019
Study protocol	12th July 2019
Study report	25th Dec 2021
Manuscripts	25th Feb 2022
Slide set	25th Feb 2022

Milestones

Milestone	April 2019	July 2019	April 2020	November 2020	June 2021	July 2021	September 2021	December 2021	February 2022
1. Preliminary study plan *	■								
2. Data specification + study protocol *		■							
3.Statistical analysis plan and final study protocol on EU-PAS			■						
4. Interim analysis **				■	■				
5. Final data extraction by data providers done					■	■	■		
6. Final data verification and transformation done						■	■		
7. Statistical analysis results ready							■	■	
8. Study report finished*								■	
9. Manuscripts and slide set drafted*									■

* Deliverables required by EMA. All other milestones are internal milestones.

** Rounds of data extraction, transformation and quality checking will be conducted throughout 2020 to facilitate an efficient final extraction in July 2021.

7. RATIONALE AND BACKGROUND

The protocol has been developed under the Framework service contract (nr. EMA/2017/09/PE/04) with regard to the re-opening of competition no.2. The topic of this proposal is to describe a study to investigate the use of valproate-containing medicinal products authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice.

7.1   BACKGROUND

Valproate and related substances (valproic acid, sodium valproate, magnesium valproate, valproate semisodium and valpromide) are licensed for the treatment of epilepsy and manic episodes in patients with bipolar disorder in Europe, in some EU Member States also for the prophylaxis of migraine.

The teratogenic risk and congenital malformations and neurodevelopmental disorders associated with the use of valproate in pregnant women is well established. Available data showed an increased incidence of both minor and major malformations in children born to mothers treated with valproate and related substances during pregnancy. The risk is dose dependent with no threshold dose below which no risk exists. Exposure to valproate *in utero* can have adverse effects on the mental and physical development of exposed children, including autism. Limited data suggests that children exposed to valproate *in utero* may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD) (Tomson et al (2011), Kellog et al (2017)).

Due to the risk of malformations and neurodevelopmental disorders of children exposed *in utero* a review in 2014 concluded that valproate and related substances should not be used to treat epilepsy in female children, women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated. Manic episodes in bipolar disorder should only be treated with valproate when lithium is contraindicated or not tolerated and the prophylaxis of migraine attacks has been contraindicated in pregnancy and women of childbearing potential not using effective methods of contraception. Warnings and precautions with updated information on the risks related to exposure during pregnancy were included in the product information of all medicinal products containing valproate and related substances, including development of educational materials for patients and healthcare professionals.

However, a European Union-level post-authorisation safety study (PASS) requested by PRAC and French national data showed that despite the 2014 risk minimisation measures a high level of exposure to sodium divalproate and valpromide among women of childbearing potential persisted and that prescribing conditions were not adhered to, especially in the bipolar disorder indication[1].

A cumulative search from the first case entered in the global pharmacovigilance database on the originator (Sanofi) to 31 May 2017 to identify all solicited and unsolicited cases of congenital malformation reported in siblings after *in utero* exposure to valproate as a suspect drug, using the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0, resulted in a total of 307 cases of congenital malformation reported in children belonging to the same family after *in utero* exposure to valproate, among a total of 2476 cases of congenital malformation.

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[1] https://www.ema.europa.eu/medicines/human/referrals/valproate-related-substances-0

Those 307 cases involved a total of 132 families. In the majority of the 132 families (n=120), there were either 2 (98/132, i.e., 74.2%) or 3 (22/132, i.e., 16.7%) children reported with a congenital malformation. All siblings in these 132 families had *in utero* exposure to valproate. It is noteworthy that the number of cases was smaller than the number of impacted children because in 4 families, only 1 case was created for all children in each of these families.

The indication for valproate treatment was epilepsy in 93.2% (286/307) of cases. The indication for valproate therapy was unknown in the remaining cases. It is therefore evident that continued use of valproate as a treatment for epilepsy by women of childbearing potential requires direct attention.

In March 2018 a referral procedure ([EMEA/H/A-31/1454](#)) under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data confirmed the already known teratogenic risk and neurodevelopmental disorders associated with the use of valproate and related substances in pregnant women. The PRAC noted insufficient adherence to the educational measures for patients and healthcare professionals introduced in 2014 which did not reach the targeted audience in a satisfactory rate and usage data indicated that valproate is still used by a considerable proportion of women of childbearing potential for both epilepsy and bipolar disorder indications.

7.2 PREGNANCY PREVENTION PROGRAM

To effectively prevent valproate exposure during pregnancy the PRAC required the implementation of a pregnancy prevention programme (PPP) and amendments to sections 4.2, 4.3, 4.4 and 4.6 of the Summary of Product Information (SmPC), including a boxed warning and Quick Response (QR) code in the package leaflet and a visual reminder on the outer packaging that the product can harm the unborn child and that effective contraception must be used.

For all indications (epilepsy, bipolar disorders and prophylaxis of migraine attacks) valproate and related substances were contraindicated in women of childbearing potential unless the conditions of a pregnancy prevention programme, which has to be implemented in all EU Member States, are fulfilled. Valproate treatment was contraindicated during pregnancy for the indication bipolar disorders and prophylaxis of migraine attacks, and for the indication epilepsy unless there are no suitable treatment alternatives. In addition, valproate treatment should only be initiated and supervised by a specialist in the management of epilepsy, including annual treatment reviews and should only be prescribed as monotherapy and at the lowest effective dose.

In section 4.6 of the SmPC new recommendations were included in case of pregnancy and pregnancy planning that require specialist consultation on switching to alternative treatment options prior to conception, and before contraception is discontinued, or discontinuation of valproate treatment.

As part of the PPP, the PRAC required the assessment of the potential for pregnancy in all female patients undergoing valproate treatment and of the understanding and acknowledgment of the risks of congenital malformations and neurodevelopmental disorders, the need for pregnancy testing prior to initiation and during treatment, the need to use effective contraception without interruption during the entire duration of treatment with valproate, the need for at least annual treatment reviews by a specialist, the need for consultation on planning pregnancy and switching to alternative treatment options prior to conception, and before contraception is discontinued, and the need for urgent physician consultation in case of pregnancy during valproate treatment. The PRAC revised the educational materials which include a healthcare professional guide, a patient guide tailored to age and situations in a woman's life-time, a patient reminder card (attached to the outer carton to support pharmacist advice at dispensing) and an

annual risk acknowledgement form with a checklist for prescribers and for patients or carers. These materials should be made available in all EU Member States where valproate and related substances are licensed. The PRAC also required a direct healthcare professional communication (DHPC) to ensure healthcare professionals and patients are informed about the risks associated with valproate in pregnant women and women of childbearing potential and on the new measures necessary to minimise the risk of exposure on valproate in pregnancy.

7.3 FURTHER INFORMATION

PRAC also imposed post-authorisation safety studies (PASS) to assess risk minimisation effectiveness, including prescribing and switching patterns in clinical practice and patient and healthcare professional awareness of the PPP and revised educational materials. This study is complementary to the studies imposed on marketing authorisation holders of medicines containing valproate and related substances.

A search on the EU PAS database returned one PASS protocol (EUPAS19162) as of yet (November 2018). The purpose of EUPAS19162 study is to describe utilization of valproate in the general population in 3 European countries (France, Germany, and UK) and is conducted by EMA.

8. RESEARCH QUESTION AND OBJECTIVES

EMA has requested to conduct an analysis on the use of valproate-containing medicinal products authorized in the EU before and after implementation of the 2018 revised measures for PPP.

Objective 1. To determine drug utilisation and prescription patterns of valproate-containing medicinal products (ATC codes: N03AG01, N03AG02) in females of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred. This following will be described:

1.1.   Prescription of medicinal products containing valproate and related substances, by indication (i.e. epilepsy, bipolar disorder and migraine prophylaxis), by incident and prevalent users, by age group, by dose (regimen), by duration and by country (data source);

1.2.   Discontinuation of medicinal products containing valproate and related substances, by indication, by age group, by dose, by reason for discontinuation (i.e. pregnancy wish, pregnancy, adverse reactions, other), by duration and by country;

1.3.   Time trends in the prescription of medicinal products containing valproates over a minimum of at least three years before the regulatory intervention in each country and, where possible, including data up to 2020;

Objective 2. To determine prescribers' compliance with recommendations included in sections 4.2, 4.3, 4.4 and 4.6 of the SmPC for valproate-containing medicinal products (see Annex II), by indication (i.e. epilepsy, bipolar disorder and migraine prophylaxis), by age group, by dose, by duration and by country;

Objective 3. To determine, in so far as is possible, patients' use of effective contraception in compliance with sections 4.4 and 4.6 of the SmPC for valproate-containing medicinal products (see Annex II), by indication (i.e. epilepsy, bipolar disorder and migraine prophylaxis), by age group, by method of contraception and by country. As a direct measure of lack of effective contraception and resultant problems, pregnancies occurring during valproate exposure will be examined;

Objective 4. To determine drug utilisation and prescription patterns over time for alternative medicines (with particular focus on the whole class of antiepileptic medicines) prescribed in females of childbearing potential or females becoming pregnant where medicinal products containing valproate and related substances had previously been prescribed or discontinued, by indication, by age group and by country;

Objective 5. Synthesis of the results of above objectives, to draw conclusions over the effectiveness of the 2018 risk minimisation measures in terms of:

5.1.   Appropriate use of medicinal products containing valproate and related substances in females of childbearing potential in line with SmPC recommendations;

5.2.   Appropriate use of pregnancy testing prior to treatment initiation, during treatment and after stopping treatment;

5.3.   Use of effective contraception in females of childbearing potential exposed to valproate and related substances;

5.4.   Incidence of pregnancies in females of childbearing potential exposed to valproate and related substances.

9. RESEARCH METHODS

9.1 STUDY DESIGN

The study design for the will be a cross-sectional time series study, where outcomes (drug utilization, pregnancy prevention measures, pregnancy) are assessed every month. An interrupted time series analysis will be conducted for hypothesis testing.

9.2 Setting

The study will be conducted in childbearing potential females (age 12-55 years) between 01 January 2010 and 31 December 2020. Data from five sources are included: the Netherlands (sample, nationally representative), United Kingdom (sample, nationally representative), Denmark (national), Italy (regional database, Tuscany) and Spain (multiple regions), covering a source population of over 30 million people (approximately 8 million women of childbearing age). More details are provided in section 9.4. All databases capture GP prescribing and 3 also capture specialist prescriptions, allowing us to explore this as a reason for differences between databases. The Italian administrative database has difficulty assessing oral contraceptives, as these are not reimbursed. Instead, for this cohort, only invasive pregnancy prevention methods will be measured (e.g. hysterectomy, sterilization).

Entry into the cohort

Women will enter the cohort on the latest of the following dates: 01 January 2010 having one year of previous valid data, the twelfth birthday, database registration.

Exit from the cohort

Cohort exit will be the earliest of 01 January 2020, the 56th birthday, database deregistration, death.

Table 1   Overview of databases to be used for the study

Characteristic	PHARMO Nationally representative	CPRD (HES-linked) Nationally representative	Danish National Registries*	ARS Tuscany	BIFAP Multi-regional
Handling partner	PHARMO	LSHTM	UCPH	ARS	AEMPS
Country (population size, millions)	Netherlands (17.0)	UK (66)	Denmark (5.8)	Italy (59.8)	Spain (46.5)
Type of database	EMR	EMR	ADM	ADM	EMR
No. active patients in database, millions	4.2 (prior to linkage)	10.0	5.8	3.6	9
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Updates	Annual	6 monthly	Annual	Monthly	Annual
Valproate Rx					
GP Rx	Yes	Yes	Yes	Yes	Yes
Outpatient Rx	Yes	No	Yes	Yes	No
Private Rx	No	No	Yes	No	No
Inpatient hospital Rx	Yes (not used here)	No	No	No	No
Date of Rx	Yes	Yes	Yes	Yes	Yes
Quantity of Rx	Yes	Yes	Yes	Yes	Yes
Duration of Rx	Yes	Yes	Yes	Based on DDD	Yes
Daily dose	Yes	Yes	Yes	Based on DDD	Yes
Brand/generic	Yes	Yes	Yes	Yes	Yes

Registered diagnosis compatible with indication of valproate	Diagnosis codes in history	Read diagnosis as a proxy	Diagnosis codes in history	Diagnosis codes in history	Linked to prescription and diagnosis codes in history
Coding of drugs	ATC	Gemscript/BNF product codes	ATC	ATC	ATC
Dosing regimen	Yes	Yes (incomplete)	No	No	Yes
Pregnancy testing	No (mainly OTC)	Yes	No	No	Yes
Pregnancy prevention					
Oral contraceptives	Yes	Yes	Yes	No	Yes (only those reimbursed)
Duration OC	Yes	Yes	Yes (based on DDDs)	No	Yes
Intrauterine device/system					
Date fitted	Yes	Yes	Yes (not copper IUD)*	No	No
Date removed	Yes	No	No	No	No
Implanon/Nexplanon/ etonogestrel					
Date inserted	Proxy based on date of prescription fill	Yes	Date of prescription fill	No	Not systematically
Date removed	Proxy based on date of prescription fill	No	No	No	Not systematically
Noristerat/norethiste rone enantate					
Date injected	Not marketed	Yes	Not marketed	No	Yes
Depo-provera					
Date injected	Proxy based on date of prescription fill	Yes	Date of prescription fill	No	Yes
Written record of OC advice	Free text, if recorded by GP	Yes (partial)	No	No	Free text potentially
Hysterectomy	Yes	Yes (HES linkage)	Yes*	Yes	If record. by GP
Oophorectomy	Yes	Yes (HES linkage)	Yes*	Yes	If record. by GP
Sterilisation	Yes	Yes (HES linkage)	Yes*	Yes	If record. by GP
Partner vasectomy	No	No	No	No	No
Completed Menopause	Free text potentially	No	No	No	If record. by GP and free text potentially
Outcomes					
Reasons for stopping Valproate	No	No	No	No	Free text potentially
Coding of disease	ICPC, ICD-9, ICD-10	CPRD: Read HES: ICD-10 and OPCS-4	ICD-10*	ICD-9 CM/ICD-10	ICPC-2, ICD-9
Pregnancy outcomes	Linkage to perinatal registry	Mother-Baby Link via algorithm in CPRD	Linkage to birth register*	Linkage to birth register, hospitalization, mental health registry	From mother's records, if recorded by the GP
Number of pregnancies per year	29000 linked pregnancies / year	Not yet known	60.000 births/year	Not yet known	Not yet known

ADM = Administrative; ATC = Anatomical Therapeutic Chemical; EMR = Electronic Medical Records; ICD= International Classification of Disease, ICPC = International Classification of Primary Care. DDD=defined daily dose

* Due to data access delays for the Danish National Registers, diagnosis, procedure and pregnancy information will not be available during the study; only information on prescriptions will be available

9.3 VARIABLES

9.3.1 EXPOSURE DEFINITION

The main exposure for objectives 1-5 is valproate-containing medicinal products (ATC and BNF product codes are listed in Annex I):

- Valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, valproate bismuth, calcium valproate, valproate magnesium).

Operationalization

Prescriptions or dispensing events will be extracted from drug files by ATC/CPRD product code or product name. A list of nationally authorized products is available in Annex I.

Valproate users will be classified as prevalent users if valproate was already prescribed in the year prior to start of follow-up, defined as January 1, 2010 or date of entry into the database (after Jan 1, 2010), whichever is earliest. Otherwise, the first episode of valproate use will be classified as incident.

Treatment episodes will be constructed following existing methodology (Gardarsdottir et al (2010)). An episode for a product with a given ATC/BNF code will start on the date of incident prescription/ dispensing. A tailored software package (AdhereR) (Dima et al 2017) will be used to investigate different periods between prescriptions for definition of discontinuation (30 days and 90 days – see Sensitivity analyses below) as well as construction of treatment periods for stratification by prior duration use.

The theoretical duration of each prescription will be estimated based on the preferred method for each individual database. Each data access partner (DAP) will recommend the approach that is expected to minimize exposure misclassification in their database, given their available data. For example, this may be based on the number of units prescribed/dispensed and the dosage regimen (prescribed daily dose), or, when information on dosage regimen is missing , based on either the typical period for duration of a prescription for chronic diseases in the country (e.g., 30 or 7 days) or the duration based on the assumption that one defined daily dose (DDD) will be used per day . The algorithms used for each database and rationale will be reported in the final report and manuscript. Overlap between prescription refills of a specific valproate (i.e. a prescription refill with the same ATC/BNF code is given before the previous prescription runs out) will be accounted for by adding the overlapping days to the end of the treatment episode (Figure 1). An upper bound of 30 days will be set, so that overlap that is added cannot exceed this limit. Discontinuation of valproates will be defined as no record of prescription/dispensing within 90 days following the theoretical end of the last valproate prescription within a valproate episode.

Figure 1: The construction of treatment episodes for valproates (Gardarsdottir et al (2010))

TE: treatment episode

Duration of use

Duration of use will be defined as the time from initiation of treatment based upon the first recorded prescription or dispensing in the look-back or study periods until discontinuation or switch to an alternative medication (see definition for switching below). Females meeting criteria for discontinuation may re-initiate, leading to multiple episodes of treatment. Treatment duration, per episode will be stratified as follows: < 6 months, 6 months to < 1 year, 1 year or more.

Dose

Dose information will be extracted as recorded in each database. Due to a lack of availability of information on plasma concentration levels of valproate and heterogeneity in the testing of blood plasma between clinicians and countries, where available, dose information will be extracted from prescription/dispensing files. Although valproate dosing is expected to vary across episodes (information on this will be extracted if available in the databases), the dose of primary interest will be the starting dose prescribed/dispensed.

Alternative medications (Objective 4)

We will identify alternative treatments used by valproate-users during and after discontinuing valproate (ATC and BNF codes are listed in Annex I):

Alternatives for epilepsy treatment

- Carbamazepine, phenobarbital, phenytoin, primidone, clobazam, clonazepam, eslicarbazepine acetate, lamotrigine, oxcarbazepine, perampanel, rufinamide, topiramate, zonisamide, brivaracetam, ethosuximide, gabapentin, lacosamide, levetiracetam, pregabalin, tiagabine, vigabatrin.

Alternatives for bipolar disorder treatment (maintenance)

- Lithium, quetiapine, olanzapine or lamotrigine.

Alternatives for migraine prophylaxis

- Beta-blocker, topiramate, amitriptyline, flunarizine, pizotifen, clonidine.

Operationalization

The occurrence of switches from valproate to alternative medications will be defined as the occurrence of a prescription of an alternative medication during the period of theoretical duration for the last prescription/dispensing in a valproate episode or within the 90-day period of discontinuation (see Figure 2 for details). If a record for valproate occurs on the same date as an alternative medication, this will be classified as concomitant use and will be considered separately in the analysis. If a prescription of an alternative medication occurs after valproate discontinuation (after 90 days of the episode end), this will not be considered as a switch.

Figure 2: Definition of the period in which treatment switching can occur
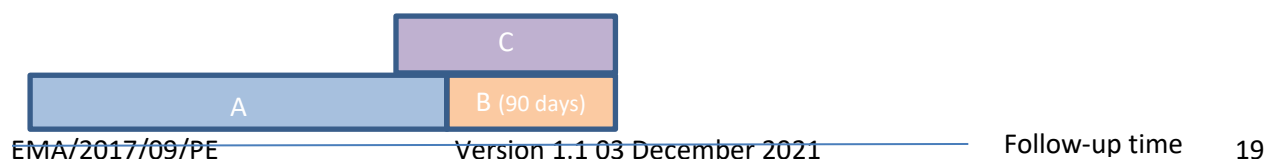
A. Treatment episode (valproate).
B. Discontinuation period (90 days). If a patient does not restart valproate treatment within 90 days of the theoretical end of a treatment episode, they are considered to have discontinued treatment.
C. Period during which prescription of an alternative medication will be considered as a "treatment switch".

Locally the extracted prescription/dispensing data will be transformed into a common input file structure on prescriptions. See the Exposures CDM table in Annex III.

9.3.2 OUTCOMES

Reason for discontinuation (Objective 1)

Operationalization

The reason for discontinuation will be assessed by review of GP records and categorized as pregnancy wish, pregnancy, adverse reaction (tremor and nausea), multiple or unknown during the 3 months preceding discontinuation. Due to a lack of available free-text information in the contributing data bases, reasons for discontinuation will be based on coded information.

Pregnancy wish will be coded as the reason for discontinuation if a female is prescribed folic acid during a treatment episode which ends with discontinuation according to discontinuation criteria or 90 days after discontinuation.

Pregnancy will be assumed as the reason for discontinuation if a pregnancy event is observed during a treatment episode which ends with discontinuation according to discontinuation criteria.

Adverse reactions will be assumed if a known valproate-associated ADR event is recorded during an exposure period which ends with discontinuation according to discontinuation criteria. ADRs with classification of "very common" (>1/10) in the SmPC for valproate will be considered (see Annex II, SmPC section 4.8 Undesirable Effects). As a result, nausea and tremor will be investigated as ADRs and reasons for discontinuation (see Annex IV for mapping of codes).

Because specific codes for drug ineffectiveness do not exist in the coding systems used by the data sources in this study and ineffectiveness cannot be assumed from repeated codes for drug indications, ineffectiveness will not be assessed. Rather, all discontinuations not meeting criteria specified above for pregnancy, pregnancy wish, and adverse reaction will be classified as 'unknown'.

Women who meet multiple of these criteria will be considered separately.

Pregnancy testing (Objective 2)

Operationalization

Pregnancy testing is defined as health care professional-witnessed pregnancy test. Recorded pregnancy testing will be obtained from the electronic medical records of GPs. Pregnancy testing will be labelled as appropriate (objective 5) if pregnancy testing is performed prior to initiation of treatment (incident users) and during treatment. A list of codes for pregnancy testing can be found in Annex IV.

Timing

Pregnancy testing will be defined as prior to initiation of treatment if a code for testing is recorded up to 90 days prior to valproate initiation. Testing during valproate use will be defined as a test code recorded

within a constructed valproate treatment episode.

Contraceptives measures (Objective 3)

Effective contraception is defined as at least one user independent method applied by the woman (permanent or non-permanent), or a hormone based method combined with a barrier method. The barrier method cannot be assessed reliably so will not be considered. Instead, we prefer to assess ineffective use, which can be done with more certainty. Ineffective: absence of any prescribed hormonal contraception (G03AA, G03AB, G03AC, permanent method (hysterectomy) and user-independent non-permanent measure (G02BA). See Annex I for ATC and BNF codes for contraceptive methods and Annex IV for mapping of codes for hysterectomy, sterilization and intrauterine devices. Episodes of contraception will be constructed using the individual schemes of dosing and effect duration described below.

Barrier, user dependent methods:
Contraceptive diaphragm or cap, male condom, female condom will not be ascertainable from data sources.

Hormone based user dependent methods
Vaginal ring (21 days, one week off), contraceptive patch (weekly for 3 weeks, one week off), progestogen only pill or desogestrel progestogen-only pill (28 days continuously), combination pills (21 days one week off). Based upon ATC/BNF codes, prescription dates, and units prescribed for each hormone based user dependent method, contraception coverage episodes will be constructed, taking into account duration of effectiveness for each method.

User independent non-permanent methods
Contraceptive implant (progestogen releasing: 3 years), contraceptive injection (progestogen releasing 8-13 weeks), intrauterine device (coil: 5-10 years), intrauterine system (progestogen releasing 3-5 years). Based upon ATC/BNF and procedure codes, prescription dates, and units prescribed for each user independent non-permanent method, contraception coverage episodes will be constructed, taking into account duration of effectiveness for each method.

User independent permanent methods
Female sterilization and hysterectomy. Because the data sources used do not allow for family linkage, male partner sterilization (vasectomy) will not be considered. All observation time following occurrence of a procedure or diagnosis code for female sterilization or hysterectomy will be classified as a period of contraception coverage.

Pregnancy (Objective 3)

Operationalization
A woman is considered to be pregnant if she reports a pregnancy to the GP/obstetrician, which is confirmed by a positive pregnancy test, ultrasound, or linkage with a birth record. To properly identify pregnancies across databases, e will apply a pregnancy algorithm developed by Gini R., *et al* within the framework of the ConcePTION project (ref). This builds directly on top of a published algorithm for detecting pregnancies by Matcho et al. (ref) .

Briefly, the proposed pregnancy algorithm allows the identification of past and ongoing pregnancies from 4 main streams: perinatal or birth registries, administrative data banks using diagnosis codes,

European registry of congenital abnormalities (EUROCAT) and a tailored-combined stream, which will uses additional data from medical observations (itemsets). Within this framework, three of the five participating databases are able to identify pregnancies through linkage to a perinatal or birth register (PHARMO, CPRD, ARS). In all the other databases, pregnancies will be identified using an algorithm. The stream aiming to identify diagnosis codes is based in the algorithm published by Matcho et al. (Matcho et al (2018)

The Matcho et al. based algorithm uses identification of pregnancy outcomes as a first step in pregnancy identification. Briefly, the algorithm first detects any record of live birth, stillbirth, ectopic pregnancy, abortion, or delivery. These events then represent the set of pregnancies in the data source and pregnancy start dates are assessed for each of these pregnancy outcomes using LMP, recorded gestational age, and fertility procedure, ultrasound, amniocentesis, amenorrhea, and pregnancy test dates. The algorithm therefore does not capture any pregnancies for which an outcome has not been recorded. In this study, the Matcho algorithm will be extended to account for specific features of the included data sources by mapping the codes to specific pregnancy concepts, allowing the investigators to differentiate between different types of pregnancy outcome, and by incorporating additional ICD and SNOMED codes from the BIFAP pregnancy algorithm (Sanchez Ortiz et al 2020).

9.3.3 OTHER VARIABLES

Indication of use (**Objectives 1-4**)

Operationalization
Valproate may be indicated for epilepsy, bipolar disorder or migraine prophylaxis. We will use the documented ICD/Read/ICPC-coded diagnosis (±3 months between diagnosis date and valproate treatment date) in the databases as a proxy of the indication (see Annex IV for codes). In the absence of an indication in the +/- 3-month window, earlier records will be examined to identify the likely indication. If the likely indication cannot be determined, the indication will be labeled as the category "unknown". Women with more than one of the indications of interest will be reported separately.

Age (Objectives 1-4)

Operationalization
Age of the women will be calculated from date of birth and categorized as 12-20, 21-30, 31-40, 41-55 years. For study baseline measurements, a woman's age will be defined as the year of entry into the study. For objectives 1-4, age will be defined as the age at which the outcome occurs (e.g. age determined by year of valproate exposure episode or year of pregnancy).

Country (Objectives 1-4)

Operationalization
Country will be coded as a categorical variable and labelled according to countries from which the data sources are derived.

Appropriate of use of valproates (Objective 5)

Operationalization
According to the new measures endorsed by the CMDh (21 March 2018), appropriate use of valproate-containing medicines is defined as follows:

Appropriate use in *pregnant women*

- Use for epilepsy if alternative effective treatment is not an option

Appropriate use in women of childbearing potential

- Assessment of childbearing potential prior to treatment
- Pregnancy testing before and during treatment.
- Counselling over risks of using valproate-containing products
- Annual treatment review by a specialist and reading of a risk acknowledgement form

These definitions are not all captured within electronic health records. Therefore, for Objective 5, an overall assessment of the effectiveness of the 2018 risk minimization measures will be made based on the results of the analyses within objectives 1-4. Descriptive findings will be interpreted in accordance with the definition of appropriate and inappropriate use according to the CMDh (21 March 2018), as far as possible given the data available within the included databases. No additional data analysis will be performed for this objective.

9.3.4 PRAC INTERVENTION

Although EMA released a statement on the recommendations and PPP in March 2018, the start and duration of implementation varied across regions and between products. The dates of the first and last actions in the implementation of the PPP across the regions included in this study, as gathered by the EMA, are presented below in Table 2 (see Annex V for the full information received by EMA from the participating countries).

Table 2 Start and end dates of the implementation of the PPP, per country

Country	Start date	End date
Netherlands	10-08-2018	12-12-2018
United Kingdom	30-04-2018	31-07-2018
Denmark	16-07-2018	11-10-2018
Italy	08-08-2018	02-10-2018
Spain	24-07-2018	01-12-2018

9.4 DATA SOURCES

9.4.1 DESCRIPTION OF DATA SOURCES

The Netherlands: PHARMO and the Netherlands Perinatal registry

The PHARMO Database Network is a population-based network of electronic healthcare databases and combines data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. Detailed information on the methodology and the validation of the

used record linkage method can be found elsewhere (van Herk-Sukel et al (2010)).

The longitudinal nature of the PHARMO Database Network system enables to follow-up more than 4 million (25%) residents of a well-defined population in the Netherlands for an average of ten years. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other available information depends on the data source. To address the objectives of the present study the following PHARMO databases will be used: General Practitioner Database, Out-patient Pharmacy Database and Pregnancy Register.

The General Practitioner (GP) Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC), which can be mapped to ICD codes, but can also be entered as free text.

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System. Oral contraceptives are mostly prescribed by GPs, but can also be obtained directly in the pharmacy, this will be captured in PHARMO as was proven before (Bezemer et al (2016)). PHARMO is listed under the ENCePP resources database (*www.encepp.eu/encepp/resourcesDatabase.jsp*).

The Netherlands Perinatal Registry (PRN) is maintained by Perined and comprises data on pregnancies, births and neonatal outcomes of births in the Netherlands, voluntarily collected by perinatal caregivers, mainly for benchmarking. For research purposes the data can be linked with the PHARMO Database Network via a trusted third party (TTP). Records include information on mothers (e.g. maternal age, obstetric history, parity), pregnancy (e.g. mode of conception, mode of delivery) and children (e.g. birth weight, gestational age, Apgar score). Diagnoses and symptoms are coded according to the Perinatal Registry code lists. For more information: www.perined.nl. Permission on a project basis is needed from PHARMO as well as Perined to obtain these data. Combined Out-patient Pharmacy and PRN data currently cover a catchment area representing 0.5 million residents for the data cut up to 2015 (to be updated). Additional linkages to the other PHARMO databases can be performed on a patient-level. Data collection period, catchment area and overlap between data sources differ. Therefore, the final cohort size for any study will depend on the data sources included.

United Kingdom: Clinical practice research datalink

The Clinical Practice Research Datalink (CPRD, comprises computerized medical records of general practitioners (GPs) from 1987 onwards. CPRD is one of the world's largest collections of primary care data, sourced from a UK-wide network of over 1,100 primary care practices. CPRD comprises two complementary databases – Gold (from practices with VISION software) and Aurum (from practices with EMIS software). Combined, they include around 10 million currently registered active patients, representative of the UK population, of whom 75% have at least 20 years of follow up. The data covers ~15% of the population. GPs play a gatekeeper role in the UK health care system, as they are responsible for primary health care and specialist referrals. Patients are affiliated to a practice,

which centralizes the medical information from the GPs, specialist referrals, hospitalisations and tests. The data recorded in the CPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, laboratory results, hospital admissions and death. The validity of a wide range of drug exposure data is routinely tested. Only those practices that meet quality standards are used for research (about 10% of the practices that send data to CPRD do not meet the quality standards). Furthermore, validation studies are conducted regularly by comparing CPRD data to written notes of general practitioners (Herret et al (2010)). A subset of CPRD records (from practices in England) are linked to the national Hospital Episode Statistics database (HES). HES is a national dataset containing data on in-patient, out-patient and emergency care from all NHS hospitals in England. Administrative details, information on ICD-10 coded clinical diagnoses and OPCS-4-coded procedures are included. Office for National Statistics (ONS) mortality data recording causes of death from death certificates are collated by ONS and routinely linked to CPRD and HES. Of relevance for this proposal, collaborative work between LSHTM and CPRD researchers has recently established a pregnancy register within the CPRD, identifying instances of pregnancy and pregnancy outcomes since 1987.

Denmark: Danish National Registries

Denmark has a tax-funded health care system ensuring easy and equal access to health care for all its citizens, and all contacts with the system are recorded in administrative and medical registers. The records carry a unique personal identification number, called the CPR-number, assigned to every Danish citizen. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers [Pedersen CB. Scan J Public Health 2011). All registers have a nationwide coverage and an almost 100% capture of contacts covering information on currently 5.8 million inhabitants plus historical information. For the purpose of the study we will obtain information from the following registries. The Danish National Prescription Registry (DNPR) includes data on all drugs dispensed from Danish pharmacies from 1995 and onwards, including dispensing date, Anatomical Therapeutic Chemical (ATC) code, product code and amount (Kildemoes et al (2011)). Sociodemographic data is available from the Danish Civil Registration System, such as gender, date of birth, migration, vital status and civil status recorded since 1968. The medical birth register contains diagnoses from hospitalization and contracts to hospital outpatient clinics that can also be used as proxy for the indication (Bliddal et al (2018), Lynge et al (2011)).

Italy: ARS

The Italian National Healthcare System is organized at regional level: the national government sets standards of assistance and a tax-based funding for each regions, and regional governments are responsible to provide to all their inhabitants. Tuscany is an Italian region, with around 3.6 million inhabitants. The Agenzia regionale di sanit`a della Toscana (ARS) is a research institute of the Tuscany Region. ARS' database comprises all the tables that are collected by the Tuscany Region to account for the healthcare delivered to its inhabitants. Moreover, ARS collects tables from regional initiatives. All the tables in the ARS' data source can be linked with each other at the individual level, through a pseudoanonymous identifier. ARS' database routinely collects primary care and secondary care prescriptions of drugs for outpatient use, and is able to link them at the individual level with hospital admissions, admissions to emergency care, records of exemptions from co-payment, dispensings of diagnostic tests and procedures, causes of death, mental health services registry. A pathology registry is available, mostly recorded in free text, but with morphology and topographic Snomed codes. Mother-child linkage is possible through the birth registry. Vaccine data is currently available but still incomplete.

Spain: BIFAP

BIFAP (Base de Datos para la Investigación Farmacoepidemiológica en Atencion Primaria), a computerised database of medical records of primary care (www.bifap.aemps.es) is a non-profit research project funded by the Spanish Agency for Medicines and Medical Devices (AEMPS). The project started in 2001 and currently includes clinical information of 6,857 physicians (5,862 General Practitioners (GPs) and 995 paediatricians). Nine participant Autonomous Region send their data to BIFAP every year. BIFAP database currently includes anonymized clinical and prescription/dispensing data from around 9 million patients representing 70% of all patients of those regions participating in the database, and 16% of the Spanish population. Mean duration of follow up in the database is 7.2 years. Diagnoses are classified according to the International Classification of Primary Care (ICPC)-2 and ICD-9 code system. A mother-child linkage has not been made so far and no private/specialist prescribing is available.

9.4.2 DATA AVAILABILITY

Due to differences in the availability of variables and the frequency of updating (see Table 1), it will not be possible to include patient follow-up until December 31st 2020 in all analyses. A summary of data availability by milestone 6 is presented in Table 3. A comprehensive matrix of the data that will be used in the analyses within each of the five objectives is presented in Table 4.

Table 3   **Data available from each data source, per objective and outcome by milestone 6.**

Data Type	Data Source	PHARMO National	CPRD National	Danish National Registries *	ARS Tuscany	BIFAP Multi-regional
		Data will be extracted up until the end of the study period (31 December 2020). Data unavailable at any time for a data source is indicated with NA				
Prescriptions	Outpatient	Q3 2021	Q2 2021	Q4 2018	Q2 2021	NA
	In-hospital	NA	NA	NA	NA	NA
Diagnoses	GP	Q3 2021	Q2 2021	Q4 2016	Q2 2021	Q2-3 2021
	Specialist outpatient	NA	NA	Q4 2016 (hospital clinics only)	NA	Q2-3 2021
	Emergency room	NA	NA	Q4 2016	Q2 2021	Q2-3 2021
	Hospitalization	Q4 2021	Q2 2021	Q4 2016	Q2 2021	Q2-3 2021
	Death record	Q4 2021	Q2 2021	Q4 2016	Q2 2021	Q2-3 2021
Free text notes	GP charts/records	Q3 2021	NA	NA	NA	Q2-3 2021
	Hospital charts	NA	NA	NA	NA	Q2-3 2021
Perinatal registry/ Birth register	With mother-child linkage	Q4 2019	Q2 2021	NA	NA	Q2-3 2021
	Without mother-child linkage	NA	Q2 2021	Q4 2016	NA	Q2-3 2021

* Due to data access delays, for the Danish National Registers only diagnostic information before the RMM period (2018) is available and prescribing information is available up until end of 2018.** Q = quarter

Table 4. Data availability for final analysis and last available data per database and objective

Database	Availability	1) Drug Utilization	2) Pregnancy Testing	3) Effective Contraception			4) Alternative medicines	4) Pregnancy
				User-dependent non-permanent	User-independent non-permanent	Permanent		
PHARMO	Available (Y/N)	Yes	Yes (mainly OTC)	Yes	Yes	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2019	Q4 2019	Q4 2019	Q4 2019	Q4 2019	Q4 2019	Q4 2019
CPRD	Available (Y/N)	Yes	Yes	Yes	Yes	No	Yes	Yes
	Last available data Q3 2021	Q4 2020	Q4 2020	Q4 2020	Q4 2020	NA	Q4 2020	Q4 2020
Danish National Registries	Available (Y/N)	Yes	No	Yes	Yes	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2018	No	Q4 2018	Q4 2018	Q4 2018	Q4 2018	No (pregnancy data is not linked to available 2018 prescribing data)
ARS Tuscany	Available (Y/N)	Yes	Yes	No	No	Yes	Yes	No
	Last available data Q3 2021	Q4 2020	Q4 2020	NA	NA	Q4 2020	Q4 2020	NA
BIFAP National	Available (Y/N)	Yes	Partially recorded	Yes	No	Yes	Yes	Yes
	Last available data Q3 2021	Q4 2019	Q4 2019	Q4 2019	NA	Q4 2019	Q4 2019	Q4 2019

* OTC: over the counter, and therefore not available

9.5 STUDY SIZE

All eligible subjects will be included in the study. Source population includes approximately 8 million women of childbearing age over the 11 year study period, divided across the contributing centres as follows:

PHARMO: >0.5 million

CPRD: ~2 million

Denmark (2010-2018): 1.6 million

ARS: ~1.4 million

BIFAP (2010-2017): 2.5 million

9.5.1 SAMPLE SIZE ESTIMATION

A minimum of 10 pre- and post-intervention time points may be required for ITS (Ramsay et al (2003)). Given an approximate date of intervention of July 01 2018, 102 monthly pre-intervention time points and 30 monthly post-intervention time points will be available, which exceeds this minimum requirement.

To examine the impact of additional factors, power calculations were conducted based on Monte Carlo simulations in Stata/SE 14.1, as previously described (Hawley et al (2019)). Simulations (100 replicates) were based on ordinary least squares linear "slope" segmented regression models, assuming a constant pre-intervention cumulative outcome incidence of 10%, 102 pre- and 30 post-intervention time points, a background 10% variation in outcome incidence across time points and a reduction in outcome incidence of 20% or 50% after intervention. The results (Figure 3) suggest the study will be sufficiently powered to detect an effect on common outcomes (incidence of prescriptions), but may be underpowered for uncommon outcomes (pregnancy). If fewer than 10 pregnancies occur during valproate use per month, there will be less than 50% power to detect an association, even if the intervention was highly effective (50% reduction in pregnancy incidence). Therefore ITS will be restricted to the main analyses of objectives 1-4, stratified by country and stratified by country and indication for prescription outcomes.

Figure 3 Empirical power calculations for given sample sizes per time point.
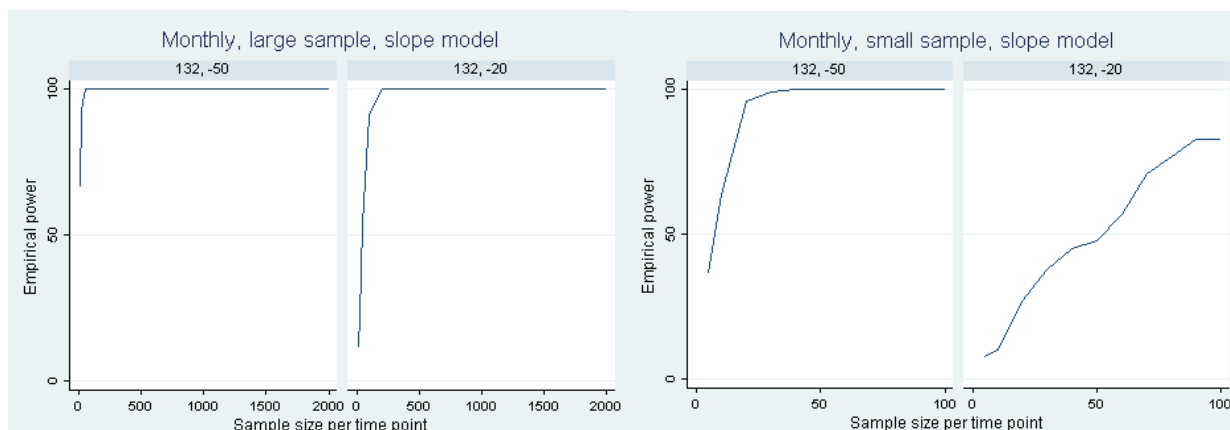
9.6 DATA MANAGEMENT

This study will be conducted using a common data model (CDM) and common analytics. This process was used successfully in several other European multi-database projects (Trifiro et al (2014)) (see figure 4). It maximizes the involvement of the data providers in the study by utilizing their knowledge on the characteristics and the process underlying the data collection and makes analysis more efficient.

First, to harmonize structure of the data sets held by each partner, a shared syntactic foundation will be built. This is described in Annex III and is referred to as the 'Level 1 CDM'. In this common data model, codes are linked to concepts but remain in their original format.

To reconcile differences across terminologies a shared semantic foundation will be built for the definition of events under study by mapping disease concepts using the Codemapper tool (Becker et al, (2017)). Based on the relevant diagnostic codes and key words (for free text search in BIFAP only), a data extraction algorithm will be constructed for each event based on the consensus of the data providers. This data extraction algorithm will then be implemented by all databases against data in the Level 1 CDM and verified using quality assessment procedures, resulting in a Level 2 CDM (see Figure 4).

Figure 4: Data management plan
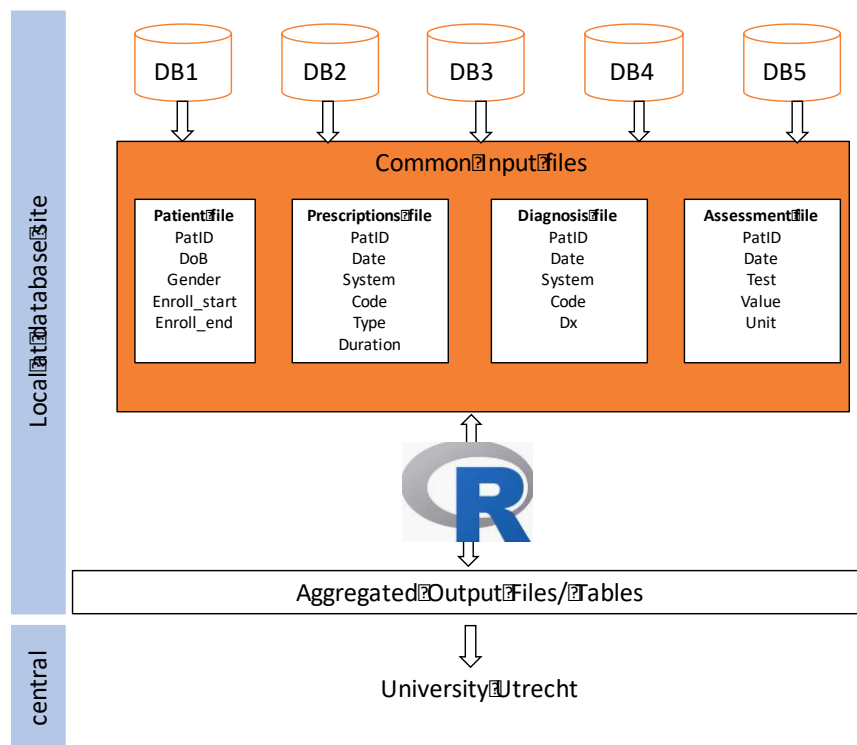
9.6.1 DATA EXTRACTION AND HARMONIZATION

Based on the agreed algorithms, each database extracts data locally using their software (Stata, SAS, R) and transforms them into a simple common data model, i.e. standardized patient, drug, measurement and event files linkable via a patient unique identifier. These data remain local.

9.6.2 Data Processing/transformation to common input files

Data processing and transformation will be conducted using R code against the common data model. The R code will be created and tested centrally and sent to the data access providers. Code will be documented for verification. The data access providers will run the R code locally and send the aggregated output to the UU server using a secure file transfer protocol. On the server, data will be further plotted and pooled (if needed) for reporting.

9.6.3 Software and Hardware

All the final statistical calculations will be done in R and/or SAS, programs will be shared with all sites for verification.

9.6.4 Storage

Processed data will be stored on YODA, Utrecht University's institutional research data repository. It is registered as such with re3data.org. YODA complies with Utrecht University's Information Security policy for data classified as public, internal use or sensitive. All YODA data is stored in at least two geographically spread locations. The data is stored and transmitted in an encrypted format.

9.6.5 Access

All researchers that need access to YODA are trained and monitored by the data management group of the Division. Data management is also responsible for granting access to file directories of specific datasets. Data analyses on aggregated data that are shared by partners will be performed on a dedicated stand-alone desktop located in the division's secure data laboratory that is only accessible by access card and access key to relevant personnel, with output data being written to the YODA platform. Access to this desktop is only possible using a university account and password. The overall scheme for data access is illustrated in Figure 5.

Figure 5: Representation of the infrastructure for data access and storage using YODA
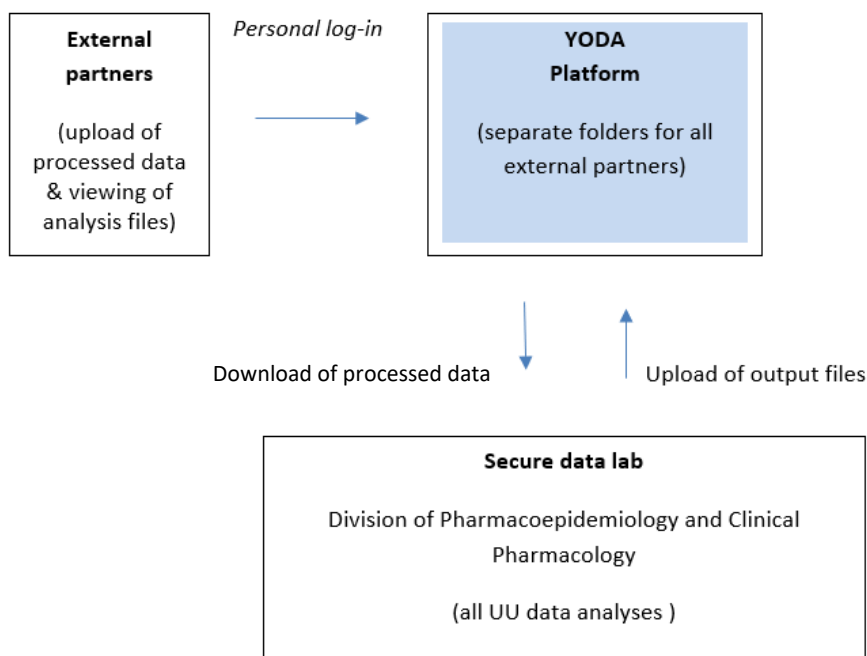
9.6.6 ARCHIVING AND RECORD RETENTION

The final study dataset and statistical programs will be archived and stored on a secured, access limited computer driver locally, as well as on the YODA platform and the divisional data management archive on the university network. The validation of the quality control (QC) of the statistical analysis will be documented. The final study protocol and possible amendments, the final statistical report, statistical programs and output file will be archived on a specific and secured drive centrally.

Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained for a period of 5 years in accordance with GPP guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement between study partners. It is the responsibility of the principal investigator to inform the other investigators/institutions as to when these documents no longer need to be retained. Study records or documents may also include the analyses files, syntaxes (usually stored at the site of the database), and questionnaires.

9.7 DATA ANALYSIS

9.7.1 ANALYSIS OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The source population and study population will be described in numbers and persontime by age, country and calendar year. Valproate users will be described on the basis of baseline characteristics (first prescription/dispensing in follow-up) with the following variables: age, indication, incident/prevalent , concomitant use of alternative treatments (prescribed before and lasting until first valproate prescription/dispensing). Frequency tables will be generated for categorical variables. The proportion of missing data for each variable will be reported as well as the proportion of treatment episodes estimated using population averages, per country.

9.7.2 STATISTICAL METHODS

Monthly period prevalence and incidence (of valproate use)

Monthly period prevalences (QPP) will be estimated and defined as the number of female valproate users of childbearing age during the month of interest (at least one day of valproate exposure) divided by the total number of women of childbearing age (with at least one day of follow-up) per month.

To quantify changes in number of incident valproate users over the study period (i.e. individuals who did not use valproate in the prior year), monthly incidence rates will be calculated as the number of female valproate initiators (as defined in section 9.3 Exposure definition) of childbearing age during the quarter of interest divided by the total number of women-of-childbearing-age-years per quarter. Incidences will be standardized by age according to the European standard population 12-55 years of age. Poisson regression will be used to estimate the 95% confidence intervals around the prevalence and incidence.

Interrupted time series analysis

To test the effect of the 2018 risk minimization measures on outcomes, interrupted time-series analyses (ITS) will be conducted. Segmented Poisson regression analysis will be used to compare the pre-intervention (2010-2018) and post-intervention (2018-2020) level and trend changes in each of the tested outcomes. The timing of intervention is defined as described in Section 9.3 Intervention. A slope and level-change impact model with two segments will be used: segment 1 will model constant pre-intervention outcome, segment 2 will model post-intervention outcomes . Regression coefficients

(interpretable as incident rate ratios), confidence intervals and p-values will be estimated. For all analyses, data will be used from January 1st 2010 until the last date of available information (see Section 9.4 for details).

Key assumptions of the Poisson regression models will be tested. First-order autocorrelation will be tested with the Durbin-Watson statistic and graphically with autocorrelation function plots (Durbin et al. (1950)). Second, overdispersion of the Poisson models will be checked according to the dispersion parameter. If overdispersion is detected, negative binomial regression models will be used instead of Poisson models for the segmented regression analyses. Finally, for the analysis of pregnancy testing, mixed-effects Poisson models (with random intercepts) will be applied to account for clustering of pregnancy testing within-prescribers.

Pooled analyses

ITS analyses will be presented separately per country, using forest plots, as well as pooled, where appropriate. After transformation to the common data model, data from each centre will be analysed together centrally in a 1-stage approach. The same time periods for implementation of the PPP intervention will be used across countries (see section 9.3), and therefore time scales will not need to be centred. Mixed effects Poisson regression models will be fitted with a random intercept and slope per country to account for between-centre heterogeneity in the baseline incidences of outcomes and the effects of the intervention. When the underlying heterogeneity in outcomes is large across countries, pooled analyses will not be conducted.

9.7.3 STATISTICAL ANALYSIS

Objective 1: Valproate use and discontinuation

The prevalence of valproate users over the study period (based on dispensing records, or when unavailable, prescription records) and incident valproate use will be estimated by MPPs and incidence rates as described in section 9.7.2. Calculations will be stratified by age categories, indication, dose, and country. In addition, MPPs will be stratified by categories of the duration of treatment episode (up until that quarter). ITS analyses will be conducted to compare i) the montlyly prevalences of valproate users and ii) the rate of incident valproate use before and after the period of intervention (as described in Section 9.7.2), stratified by country and indication, and pooled where appropriate. The ITS analysis will test the null hypotheses that there was no difference between pre- and post-intervention trends in MPPs of valproate use and incident valproate use.

To assess discontinuation, the numbers of discontinuers (as defined in section 9.3) will be counted per quarter, and the proportion of discontinuation will be calculated as the number of female who discontinued valproate within a quarter divided by the total number of valproate users in the previous period. This will be stratified by country, indication, age group, duration of treatment and reason for discontinuation (adverse drug reaction, pregnancy wish, pregnancy, other). In addition, Kaplan-Meier curves for drug "survival" (the proportion of patients still being treated after a given number of days) will be produced pre- and post-implementation of the PPP. To do this, the start of follow-up ("t = 0") will be set as the date of incident valproate prescription/dispensing. Log rank tests will be applied to test for differences between subgroups of interest (indication, age, dose, country). ITS analyses will be conducted to compare the monthly frequencies of valproate discontinuation before and after the period of intervention stratified by country and indication and pooled where appropriate.

Objective 2: Prescriber compliance

Compliance of prescribers with recommendations for valproate containing medicinal products will be analysed on a prescription level (each valproate prescription) and assessed in two separate analyses: 1) pregnancy testing confirmed by healthcare professional before valproate prescription (start of an episode) and during use and 2) prescription/implementation of contraceptive methods before and the proportion of valproate prescriptions that occurred within a period of contraception.

First, the proportions of valproate prescriptions with which a physician-confirmed pregnancy test was recorded i) up to 90 days prior to the date of prescription or dispensing and ii) 90 days following a prescription will be calculated per month year, stratified by country, indication, age group, duration and dose of valproate. An ITS analysis will be conducted to test for a change in frequency of pregnancy testing (prior to and after prescription) before and after the intervention, with time points per month year, stratified by country and indication. We will test the null hypothesis that there was no difference between trends in pregnancy test frequency in women prescribed valproates per month year pre- and post-intervention.

Second, the proportion of valproate prescriptions alongside which a contraceptive method was prescribed (within 90 days prior to the date of valproate prescription) will be calculated per month-year, stratified by country, indication, age group, duration and dose of valproate. In addition, we will calculate the proportion of valproate prescriptions that occurred during an episode of contraception (constructed as described in section 9.3), per month-year, stratified by type of contraception. An ITS analysis will be conducted to test for a change in the proportion of compliant (during a period of contraception coverage) valproate prescriptions after the intervention, with time points per month year, stratified by country and indication. We will test the null hypothesis that there was no difference between trends in compliant valproate prescriptions per month year pre- and post-intervention.

Objective 3: Pregnancy

The incidence of pregnancies during valproate use will be assessed. Pregnancies will be counted if they occurred during a valproate exposure episode. Incidence rates for pregnancy occurrence during valproate exposure will be calculated per month and stratified by country, age-group and indication. An ITS analysis will be conducted to test for a change in incidence of pregnancies during valproate exposure after the intervention, stratified by country and indication (where possible due to limited sample size). As discussed in section 9.5.1, the number of pregnancies per month may be too low for stable ITS analyses. If ITS analysis is possible, we will test the null hypothesis of no difference between trends in pregnancy rates in valproate users (number of pregnancies per half year) pre- and post-intervention.

Objective 4: Alternative medications

As for valproates in objective 1, incident and prevalent use of alternative medications in women who were prevalent users or initiators of valproate will be estimated annually and defined as the number of new users within a period and the number current users at any point during a period (respectively), and will be stratified by country, age group, indication and alternative medication. The monthly incidence of treatment switches (as defined in section 9.3) will be estimated as the number of women who switch in a month divided by the total number of valproate users in the previous quarter. ITS analyses will be conducted to test for a change in frequency of switches to alternative medications after the intervention, with time points per month year, stratified by country and indication. We will test the null hypothesis that there was no difference between trends in the frequency of switches to alternative medication in women prescribed valproates per month year pre- and post-intervention.

Objective 5: Assessment of overall effectiveness

An overall assessment of the effectiveness of the 2018 risk minimization measures will be made based on the results of the analyses within objectives 1-4. Descriptive findings will be interpreted in accordance with the definition of appropriate and inappropriate use according to the CMDh (21 March 2018), as far as possible given the data available within the included databases.

The intervention will be determined to be effective if a decrease is observed in the incidence and monthly prevalence of inappropriate use of valproates, and this is supported by findings of statistical tests for changes in the individual components: increase in the amount of contraceptive use in valproate users, increase in the amount of pregnancy testing in valproate users and a decrease in pregnancies in valproate users. The intervention will be determined to be completely successful upon evidence of a positive impact on all three outcomes or partially successful if one or two outcomes improved.

9.7.4 MISSING DATA

Since the underlying data represent attended medical care we generally assume that absence of information of clinical events means absence of that condition. No imputation will be done for missing data.

9.7.5 SENSITIVITY ANALYSIS

The following sensitivity analyses will be conducted in addition to the main analyses:

Objectives 1-4: The study period will be restricted to end at February 2020, to investigate the impact of excluding the period of time affected by the COVID-19 pandemic, which is known to have impacted on health care seeking behaviour and collection of prescriptions.

Objectives 1,4: The discontinuation period for valproate use will be reduced to 30 days when defining treatment episodes, discontinuation and switching.

Objectives 1-4: The pre-intervention time period for ITS analyses will be restricted to January 01 2015 – 01 July 2018. This will assess whether possible non-constant pre-intervention time trends (due to additional 2014 risk minimization measures) might have influenced the results of the ITT analysis.

Objective 2: The window of appropriate pregnancy testing prior to and during a valproate treatment episode will be reduced from 90 to 30 days.

Objective 2: The window for contraceptive coverage prior to prescription will be reduced from 90 to 30 days.

The sensitivity analyses will be conducted individually and not in combination.

9.8 QUALITY CONTROL

9.8.1 QUALITY MANAGEMENT

The study will be conducted according to the guidelines for Good Pharmacoepidemiology Practice (GPP) (International Society for Pharmacoepidemiology 2008) and according to the ENCePP code of conduct (European Medicines Agency 2018). All data access providers have experience in conducting pharmacoepidemiological research and research is done by researchers trained in pharmacoepidemiology. All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement. Only

validated software (R and/or SAS version 9.4, SAS Institute Inc., Cary, NC) will be used for statistical analyses

The Division of Pharmacoepidemiology & Clinical Pharmacology at Utrecht University is working according to a quality management system based on ISO 9001 principles, at the moment in development towards certification. The quality management system is system- and process-oriented and based on continuous improvement. The system is based upon standard operating procedures implemented throughout the division with regular internal audits as well as external audits that lead to certification. The quality management system is based on national and international external quality requirements where available and pertinent, including the guidelines for Good Pharmacoepidemiological Practices, ENCePP Guide on Methodological Standards in Pharmacoepidemiology, Good Clinical Practice, and Good Clinical Data management Practice as well national and international guidelines and legislation concerning data-handling and privacy issues.

9.8.2 Data quality

Data quality will be assessed according to the United States FDA Sentinel System data quality indicators[2,3]: The data quality and characterization checks described below will take place in collaboration with partners. All data will remain local and only summary measures described below will be inspected in collaboration with study statisticians. This process will proceed iteratively in collaboration with each data partner until consensus regarding acceptable data quality and fitness for purpose has been reached.

Level 1 data checks review the completeness and content of each variable in each table to ensure that the required variables contain data and conform to the formats specified by the CDM specifications (e.g., data types, variable lengths, formats, acceptable values, etc.). This is a check conducted in collaboration with partners to verify that the extract, transform, and load (ETL) procedure to convert from source data to the CDM has been completed as expected. Formats for all values will be assessed and compared to a list of acceptable formats. Missingness for core variables such as date of birth or sex will be assessed at this stage. Frequency tables of variables with finite allowable values will be created to identify unacceptable values. Counts of codes for events and exposures of interest in each data source will be tabulated.

Level 2 data checks assess the logical relationship and integrity of data values within a variable or between two or more variables within and between tables. At this stage we may check for consistency between variables such as date of delivery and date of birth for a linked mother-child pair, verify that all health encounters occur on or after a subject's date of birth, etc.

Level 3 data checks examine data distributions and trends over time, both within a Data Partner's database (by examining output by year and year/month) and across a Data Partner's databases (by comparing updated SCDM tables to previous versions of the tables). For example, a level 3 data check would ensure that there are no large, unexpected increases or decreases in records over time. In this check, we will calculate person-time in women of child-bearing potential by calendar year and database. We may also calculate incidence of valproate prescriptions by calendar year, database, and indication, as well as incidence of contraception prescriptions by contraceptive type, calendar year, and database. By

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[2] https://www.sentinelinitiative.org/sentinel/data-quality-review-and-characterization
[3] https://www.sentinelinitiative.org/sites/default/files/data/distributed-database/Sentinel_DataQAPractices_Memo.pdf

comparing these types of summary measures across data sources and over time, anomalies and errors which can be corrected in partnership with data sources may become apparent.

9.9 LIMITATIONS OF THE RESEARCH METHODS

9.9.1 LIMITATIONS RELATED TO THE DATA SOURCES

For all databases, it should be noted that the primary aim of data collection is patient management and not medical research. No single European data source contains all the information required in this study. This has several implications for this study. First, only events are collected which are deemed to be relevant for patient care. Mild cases of nausea and tremor (ADRs) might not be recorded, although in such mild cases we do not expect the symptoms to lead to discontinuation. In addition, selection bias is mitigated by the inclusion of all women of childbearing age registered in each data source at any time during the study period.

Second, although information on prescription or dispensing of valproates is expected to be captured sufficiently in each database, CPRD and BIFAP do not capture outpatient specialist prescriptions, which may result in incomplete information on alternatives to valproates. The extent to which these prescriptions are missing will be estimated during the stage of quality checks, by comparing the quarterly period prevalences of prescriptions across the databases. Nevertheless, we will be able to estimate the date of valproate discontinuation, which might be due to a switch.

A third limitation is the lack of available information on over-the-counter contraceptives, which are not captured in any of the databases. Therefore, our ability to capture oral contraceptive use (especially in Italy), will be limited, and records of barrier methods will not be available. This will result in an underestimation of the proportion of valproate episodes that meet the criteria for adequate contraceptive coverage. However, since the error is equal over time, it may lead to less power to detect a difference but not a differential error.

Fourth, we anticipate that a number of databases (such as PHARMO and the Danish National Registries), will have few records of pregnancy testing, as pregnancy tests are primarily sold over the counter. However, as the PPP explicitly calls for *physician-witnessed* pregnancy testing, we argue that records of pregnancy tests should be available if physicians have adhered to the recommendations.

A fifth issue with missing data is that not all databases will have information on all relevant outcomes up until the end of the data collection period, December 31st 2020. Data from the BIFAP database will be available up until December 31st 2019, which limits the amount of information available on Spain post-intervention. This will limit the power to detect a significant change in outcomes in the Spanish cohort in the ITS analyse. This issue will be mitigated by applying a 1-stage meta-analysis to data transformed to the common data model, providing additional power from the remaining countries with complete follow-up. Due to severe delays in access to Danish data, as a result of the prioritization of COVID-19 studies by the data holder, analyses with Danish data can only be completed in part by the date of the final deliverables. This means that only the main analyses of objectives 1, 2 and 4 can be conducted, as no information will be available in time on diagnostic or pregnancy information. In addition, the available data only extends to the end of 2018, which means limited inferences on the impact of the PPP in this data source can be drawn by the date of the final deliverable.

Sixth, the COVID-19 pandemic has likely impacted on the rates of healthcare visits and prescribing, and may have influences the behaviour of individuals when ordering repeat prescriptions. This is likely to have an impact on the trends seen from February/March 2020 onwards. To explore the impact of this,

we will conduct a sensitivity analysis (for all ITS analyses) where we end the study period at January 31st 2020.

A final challenge is the lack of free-text information available from the different sources, leaving us reliant on records of products and diagnoses. This will mainly limit our ability to determine the reasons for valproate discontinuation. While discussions of pregnancy wish may have been recorded by general practitioners, this study must rely on folic acid prescriptions as a proxy for pregnancy wish, which may have low sensitivity.

Misclassification of endpoints is possible. For the different databases that will be used, validation studies have shown that coding is reliable in the databases and that these databases are suitable for pharmacoepidemiological research (see section 9.4.1). Where possible, we will test multiple algorithms to determine outcomes, particularly for the key outcome pregnancy, for which rounds of testing and review across the centres will be completed. In addition, we anticipate that our use of prescription/dispensing records may lead to an overestimation of actual use of valproates (and other prescribed products).

9.9.2 *LIMITATIONS IN THE METHODOLOGY*

Although the ITS design is considered the best available method to evaluate the impact of policy changes where a control group is not available, causality cannot be established and causal inference is subject to key assumptions. While confounding (including residual and unmeasured confounding) is controlled for by design, other external and unmeasurable time-varying factors unrelated to the EMA PPP may influence the utilization of valproates or compliance with the PPP and cannot be accounted for. Thus the conclusions we will draw in our summary for objective 5 will need to be based on a combination of descriptive results and hypothesis testing. Finally, the PPP is not a clearly defined intervention. The staggered implementation across Europe makes it challenging to assess the impact of the PPP on the various outcomes under study. As it is not possible to fully establish precise dates of implementation in each of the countries due to variation at the regional and practice-levels, we decided to model an implementation period of 6 months for the ITS analyses, which aims to broadly capture the stepwise implementation. Nonetheless, this decision may influence the results of the ITS analysis.

10. PROTECTION OF HUMAN SUBJECTS

For this study, participants from various EU member states will process personal data from individuals which is collected in national/regional electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All of the databases used in this study are currently already used for pharmacoepidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

According to these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which will generate non identifiable data with less detailed information that will be pooled across databases.

The output files are stored at Utrecht University. These output files do not contain any data that allow identification of subjects included in the study. In fact, each record is completely anonymous and does not contain any identifier key. The protocols will be reviewed by the Institutional Review Boards (IRBs) of

the respective databases.

11. Management and reporting of adverse events/reactions

As this is a non-interventional study based on secondary use of data (from various EU electronic healthcare databases), safety monitoring and safety reporting, where there is a safety relevant result, is provided on an aggregate level only; no reporting on an individual case level is required. In studies based on secondary use of data with a safety relevant result, reports of adverse events/adverse reactions should be summarized in the study report, i.e. the overall association between an exposure and an outcome.

12. Plans for disseminating and communicating study results

Upon study completion and finalization of the study report, the results of this non-interventional study will be submitted for publication and posted in the EU PAS publicly accessible database of results. Publications will comply with the International Committee of Medical Journal Editors (ICMJE) guidelines.

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ANNEXES

ANNEX I: MAPPING OF PRODUCTS TO ATC/BNF CODES

Table I.1   Valproate-containing products authorized by the included countries

Product	Authorization country
Depakin	Italy
Depakin Chrono	Italy
Depakine	Spain, Netherlands
Depakine Chrono	Spain, Netherlands
Depakine Chronosphere	Netherlands
Depakine Enteric	Netherlands
Depakote	United Kingdom
Depamag	Italy
Depamide	Italy, Spain
Deprakine	Denmark
Epilim	United Kingdom
Episenta	United Kingdom
Natriumvalproaat Chrono	Netherlands
Orfiril	Denmark, Netherlands
Orfiril Cr	Netherlands
Orfiril long	Denmark
Orfiril Retard	Denmark
Sodium Valproate	United Kingdom

* List obtained from https://www.ema.europa.eu/en/documents/psusa/valproic-acid/sodium-valproate/valproate-pivoxil/valproate-semisodium/valpromide/valproate-bismuth/calcium-valproate/valproate-magnesium-list-nationally-authorised-medicinal-products-psusa/00003090/2015_en.pdf

Table I.2 Mapping of valproate exposures to ATC/BNF codes

Substance name	ATC code	BNF code
Valproic acid	N03AG01	040801020 0402030Q0
valproate semisodium		0407042A0
sodium valproate		0408010W0
Valpromide	N03AG03	

Table I.3.Mapping of alternative medicines for epilepsy to ATC/BNF codes

	Substance name	ATC code	BNF code
Epilepsy	Carbamazepine	N03AF01	0408010C
	Phenobarbital	N03AA02	0408010N
	Phenytoin	N03AB02	0408010Q
	Primidone	N03AA03	0408010U
	Clobazam	N05BA09	04080106
	Clonazepam	N03AE01	0408010F
	Eslicarbazepine acetate	N03AF04	0408010A
	Lamotrigine	N03AX09	0408010H
	Oxcarbazepine	N03AF02	0408010D
	Perampanel	N03AX22	0408010A
	Rufinamide	N03AF03	0408010A
	Topiramate	N03AX11	04080105
	Zonisamide	N03AX15	0408010A
	Brivaracetam	N03AX23	0408010A
	Ethosuximide	N03AD01 N03AD51	0408010I
	Gabapentin	N03AX12	0408010G
	Lacosamide	N03AX18	0408010A
	Levetiracetam	N03AX14	0408010A
	Pregabalin	N03AX16	0408010A
	Tiagabine	N03AG06	0408010A
	Vigabatrin	N03AG04	0408010X
Bipolar	Lithium	N05AN01	0402030K/0402030P
	Quetiapine	N05AH04	0402010A
	Olanzapine	N05AH03	04020106
	Lamotrigine	N03AX09	0408010H
Migraine	Beta-blocker: atenolol	C07AB03	0204000E
	Beta-blocker: bisoprolol	C07AB07	0204000H
	Beta-blocker: carvedilol	C07AG02	02040008
	Beta-blocker: metoprolol	C07AB02	0204000J/0204000K
	Beta-blocker: nadolol	C07AA12	0204000M
	Beta-blocker: propranolol	C07AA05	0204000R
	Beta-blocker: timolol	C07AA06	0204000V
	Topiramate	N03AX11	04080105
	Amitriptyline	N06AA09	0403010B
	Flunarizine	N07CA03	0406000E
	Pizotifen	N02CX01	0407042Q
	Clonidine	C02AC01	0407042F

Table I.4 Mapping of contraceptive methods to ATC/BNF codes

Hormone based contraceptive products (user dependent)

Vaginal ring (21 days, one week off), contraceptive patch (weekly for 3 weeks, one week off), progestogen only pill or desogestrel progestogen-only pill (28 days continuously), combination pills (21 days one week off).

Progestagens and estrogens, fixed combinations (G03AA)

Substance	ATC code	
Etynodiol and ethinylestradiol	G03AA01	07030100
Quingestanol and ethinylestradiol	G03AA02	NA*
Lynestrenol and ethinylestradiol	G03AA03	07030100
Megestrol and ethinylestradiol	G03AA04	NA
Norethisterone and ethinylestradiol	G03AA05	07030100
Norgestrel and ethinylestradiol	G03AA06	NA
Levonorgestrel and ethinylestradiol	G03AA07	07030100
Medroxyprogesterone and ethinylestradiol	G03AA08	NA
Desogestrel and ethinylestradiol	G03AA09	06040103/07030152
Gestodene and ethinylestradiol	G03AA10	07030100
Norgestimate and ethinylestradiol	G03AA11	07030100
Drospirenone and ethinylestradiol	G03AA12	06040103/07030152
Nomegestrol and estradiol	G03AA14	06040103/07030152
Chlormadinone and ethinylestradiol	G03AA15	NA
Dienogest and ethinylestradiol	G03AA16	NA
Medroxyprogesterone and estradiol	G03AA17	06040101
Cyproterone acetate and ethinylestradiol	NA	07030100
Norelgestromin and ethinylestradiol	G03AA13	07030100
Etonogestrel and ethinylestradiol	NA	06040103/07030151

*NA=no prescriptions for this drug substance in CPRD (i.e. not marketed)

Progestogens and estrogens, sequential preparations (G03AB)

Substance	ATC code	NA
Megestrol and ethinylestradiol	G03AB01	07030100
Lynestrenol and ethinylestradiol	G03AB02	07030100
Levonorgestrel and ethinylestradiol	G03AB03	07030100
Norethisterone and ethinylestradiol	G03AB04	07030100
Desogestrel and ethinylestradiol	G03AB05	07030100
Gestodene and ethinylestradiol	G03AB06	NA
Chlormadinone and ethinylestradiol	G03AB07	07030100
Dienogest and estradiol	G03AB08	07030100
Norgestimate and ethinylestradiol	G03AB09	NA

Progestagens (G03AC)

Substance	ATC code	BNF
Levonorgestrel	G03AC03	06040103/07030550
Quingestanol	G03AC04	NA
Megestrol	G03AC05	06040103/08030200
Norgestrienone	G03AC07	NA
Desogestrel	G03AC09	06040103/07030201
Drospirenone	G03AC10	NA
Dydrogesterone	G03DB01	06040102/06040103

Vaginal rings

Product	ATC code	BNF
Vaginal rings	G02BB01 G02BB01	06040101

Contraceptive patch

Product	ATC code	BNF
Norelgestromin and ethinylestradiol	G03AA13	06040103/07030101/07030100

Implant

Product	ATC code	BNF
Etonogestrel subcutaneous implant	G03AC08	06040103/07030202

Injection

Product	ATC code	BNF
Medroxyprogesterone	G03AC06	06040103/07030202

Intra-uterine devices

Product	ATC code	BNF
Plastic IUD	G02BA01	71110100/07030450
Plastic IUD with copper	G02BA02	71110100/07030450
Plastic IUD with progestogen	G02BA03	71110100/07030450

Folic Acid

Substance	ATC code	BNF
Folic acid	B03BB01	09040251
Folic acid, combinations	B03BB51	09040251
Iron, multivitamins and folic acid	B03AE02	09040251
Iron, vitamin B12 and folic acid	B03AE01	09040251

ANNEX II: INFORMATION FROM VALPROATE SmPC

Table II.1: Summary of product information sections including 2018 risk minimization measures (depakote, SANOFI, United Kingdom)[4]

SmPC section	
4.2 Posology and method of administration	Female children and women of childbearing potential Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see sections 4.3, 4.4 and 4.6). Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (see sections 4.3 and 4.4). The benefits and risks should be carefully reconsidered at regular treatment reviews (see section 4.4). Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).
4.3 Contraindications	Epilim is contraindicated in the following situations: • In pregnancy unless there is no suitable alternative treatment (see sections 4.4 and 4.6).
4.4 Special warnings and precautions for use	See Table II.2: SmPC section 4 boxed warning
4.6 Fertility, pregnancy and lactation	• Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. • Valproate is contraindicated for use in women of childbearing potential unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.4).

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[4] *https://www.medicines.org.uk/emc/product/6102/smpc*

Table II.2: SmPC section 4 boxed warning (Depakote, Sanofi, united kingdom)

4.4.1 Special Warnings

Female children, women of childbearing potential and pregnant women:

<u>Pregnancy Prevention Programme</u>

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

Depakote is contraindicated in the following situations:

• In pregnancy (see sections 4.3 and 4.6).

• In women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.6).

<u>Conditions of Pregnancy Prevention Programme:</u>

The prescriber must ensure that:

• Individual circumstances should be evaluated in each case. Involving the patient in the discussion to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.

• The potential for pregnancy is assessed for all female patients.

• The patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero.*

• The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.

• The patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.

• The patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of bipolar disorder.

• The patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.

• The patient understands the need to urgently consult her physician in case of pregnancy.

• The patient has received the Patient Guide.

• The patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

<u>Female children</u>

The prescriber must ensure that:

• The parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.

• The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero.*

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to alternative treatment before they reach adulthood.

<u>Pregnancy test</u>

Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a healthcare provider, to rule out unintended use in pregnancy.

<u>Contraception</u>

Women of childbearing potential who are prescribed valproate must use effective contraception without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case when choosing the contraception method, involving the patient in the discussion to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (mood control) when initiating, or discontinuing oestrogen-containing products.

On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

<u>Annual treatment reviews by a specialist</u>

The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss the Annual Risk Acknowledgement Form at initiation and during each annual review, and ensure that the patient has understood its content.

<u>Pregnancy planning</u>

If a woman is planning to become pregnant, a specialist experienced in the management of bipolar disorder must be consulted and treatment with valproate should be discontinued, and if needed switched to an

alternative treatment prior to conception and before contraception is discontinued.

In case of pregnancy

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. The patients with valproate-exposed pregnancy and their partners should be referred to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacists must ensure that:

• The Patient Card is provided with every valproate dispensation and that patients understand its content.

• Patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of valproate in women of childbearing potential and provide details of the Pregnancy Prevention Programme. A Patient Guide and Patient Card should be provided to all women of childbearing potential using valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a specialist experienced in the management of bipolar disorder.

Table II.3.1: Undesirable effects of valproate use (SmPC section 4.8, Depakote, Sanofi, United Kingdom)

The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

Congenital malformations and developmental disorders: (see sections 4.4 and 4.6).

Hepatobiliary disorders:

Common: liver injury (see section 4.4.1)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders:

***Very common:* nausea**

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea

The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Depakote with or after food.

Uncommon: pancreatitis, sometimes lethal (see section 4.4)

Nervous system disorders:

***Very common:* tremor**

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

Uncommon: coma*, encephalopathy*, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:

Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*

Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

*These ADRs are principally observed in the paediatric population.

Metabolism and nutrition disorders:

Common: hyponatraemia, weight increased*

*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

Rare: hyperammonaemia* (see section 4.4.2), obesity

*Cases of isolated and moderate hyperammonaemia without change in liver function tests may occur, but they are usually transient and should not cause treatment discontinuation. However, they may present clinically as vomiting, ataxia, and increasing clouding of consciousness. Should these symptoms occur Depakote should be discontinued.

Hyperammonaemia associated with neurological symptoms has also been reported (see section 4.4.2). In such cases further investigations should be considered.

Endocrine disorders:

Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)

Rare: hypothyroidism (see section 4.6)

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia (see section 4.4.2)

Uncommon: pancytopenia, leucopenia

Rare: bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Depakote has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see section 4.6).

Skin and subcutaneous tissue disorders:

Common: hypersensitivity, transient and/or dose related alopecia (hair loss), nail and nail bed disorders. Regrowth normally begins within six months, although the hair may become more curly than previously.

Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:

Common: dysmenorrhea

Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:

Common: haemorrhage (see sections 4.4.2 and 4.6)

Uncommon: vasculitis

Eye disorders:

Rare: diplopia

Ear and labyrinth disorders:

Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:

Common: urinary incontinence

Uncommon: renal failure

Rare: enuresis, tubulointerstitial nephritis, reversible Fanconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Depakote therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:

Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:

Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Depakote. The mechanism by which Depakote affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2)

Respiratory, thoracic and mediastinal disorders:

Uncommon: pleural effusion

Investigations:

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: myelodysplastic syndrome

Table II.3.2: Undesirable effects of valproate use (SmPC section 4.8, Epilim 200, Sanofi, United Kingdom)

The following CIOMS frequency rating is used, when applicable: Very common (≥ 1/10); common (≥ 1/100 to ≤ 1/10); uncommon (≥ 1/1,000 to ≤ 1/100); rare (≥ 1/10,000 to ≤ 1/1,000); very rare (≤ 1/10,000); not known (cannot be estimated from the available data).

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Common: liver injury (see section 4.4.1)

Severe liver damage, including hepatic failure sometimes resulting in death, has been reported (see sections 4.2, 4.3 and 4.4.1). Increased liver enzymes are common, particularly early in treatment, and may be transient (see section 4.4.1).

Gastrointestinal disorders:

Very common: **nausea**

Common: vomiting, gingival disorder (mainly gingival hyperplasia), stomatitis, gastralgia, diarrhoea

The above adverse events frequently occur at the start of treatment, but they usually disappear after a few days without discontinuing treatment. These problems can usually be overcome by taking Epilim with or after food.

Uncommon: pancreatitis, sometimes lethal (see section 4.4)

Nervous system disorders:

Very common: **tremor**

Common: extrapyramidal disorder, stupor*, somnolence, convulsion*, memory impairment, headache, nystagmus

Uncommon: coma*, encephalopathy, lethargy* (see below), reversible parkinsonism, ataxia, paraesthesia, aggravated convulsions (see section 4.4)

Rare: reversible dementia associated with reversible cerebral atrophy, cognitive disorder

Sedation has been reported occasionally, usually when in combination with other anti-convulsants. In monotherapy it occurred early in treatment on rare occasions and is usually transient.

*Rare cases of lethargy occasionally progressing to stupor, sometimes with associated hallucinations or convulsions have been reported. Encephalopathy and coma have very rarely been observed. These cases have often been associated with too high a starting dose or too rapid a dose escalation or concomitant use of other anti-convulsants, notably phenobarbital or topiramate. They have usually been reversible on withdrawal of treatment or reduction of dosage.

An increase in alertness may occur; this is generally beneficial but occasionally aggression, hyperactivity and behavioural deterioration have been reported.

Psychiatric disorders:

Common: confusional state, hallucinations, aggression*, agitation*, disturbance in attention*

Rare: abnormal behaviour*, psychomotor hyperactivity*, learning disorder*

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*Weight increase should be carefully monitored since it is a factor for polycystic ovary syndrome (see section 4.4).

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Uncommon: Syndrome of Inappropriate Secretion of ADH (SIADH), hyperandrogenism (hirsutism, virilism, acne, male pattern alopecia, and/or androgen increase)

Rare: hypothyroidism (see section 4.6)

Blood and lymphatic system disorders:

Common: anaemia, thrombocytopenia, (see section 4.4.2)

Uncommon: pancytopenia, leucopenia

Rare: bone marrow failure, including red cell aplasia, agranulocytosis, anaemia macrocytic, macrocytosis

The blood picture returned to normal when the drug was discontinued.

Isolated findings of a reduction in blood fibrinogen and/or an increase in prothrombin time have been reported, usually without associated clinical signs and particularly with high doses (Epilim has an inhibitory effect on the second phase of platelet aggregation). Spontaneous bruising or bleeding is an indication for withdrawal of medication pending investigations (see section 4.6).

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Uncommon: angioedema, rash, hair disorder (such as abnormal hair texture, hair colour changes, abnormal hair growth)

Rare: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome

Reproductive system and breast disorders:

Common: dysmenorrhea

Uncommon: amenorrhea

Rare: male infertility, polycystic ovaries

Very rarely gynaecomastia has occurred.

Vascular disorders:

Common: haemorrhage (see sections 4.4.2 and 4.6)

Uncommon: vasculitis

Eye disorders:

Rare: diplopia

Ear and labyrinth disorders:

Common: deafness, a cause and effect relationship has not been established.

Renal and urinary disorders:

Common: urinary incontinence

Uncommon: renal failure

Rare: enuresis, tubulointerstitial nephritis, reversible Falconi syndrome (a defect in proximal renal tubular function giving rise to glycosuria, amino aciduria, phosphaturia, and uricosuria) associated with Epilim therapy, but the mode of action is as yet unclear.

General disorders and administration site conditions:

Uncommon: hypothermia, non-severe peripheral oedema

Musculoskeletal and connective tissue disorders:

Uncommon: bone mineral density decreased, osteopenia, osteoporosis and fractures in patients on long-term therapy with Epilim. The mechanism by which Epilim affects bone metabolism has not been identified.

Rare: systemic lupus erythematosus, rhabdomyolysis (see section 4.4.2)

Respiratory, thoracic and mediastinal disorders:

Uncommon: pleural effusion

Investigations:

Rare: coagulation factors decreased (at least one), abnormal coagulation tests (such as prothrombin time prolonged, activated partial thromboplastin time prolonged, thrombin time prolonged, INR prolonged) (see sections 4.4 and 4.6)

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Rare: myelodysplastic syndrome

* Very common reactions are highlighted in bold text.

ANNEX III: LEVEL 1 COMMON DATA MODEL, SYNTACTIC HARMONIZATION

Description

This study will make use of the ConcePTION CDM, version 2.2 - available to view here:
https://docs.google.com/spreadsheets/d/1hc-TBOfEzRBthGP78ZWIa13C0RdhU7bK/edit#gid=413205035). **METADATA** – contains general information about how the local data fit the CDM are contained: for instance, they are used to describe which tables of the standard CDM are populated in this instance; and what coding systems are used for the various data domains. This information is used by the scripts for quality check (e.g. check that all the tables that are expected to be findable can indeed be found; and that the coding systems that are observed in the data are indeed those listed here.

CDM_SOURCE - In this table, a high-level, machine-readable description of the instance of the CDM is contained. The scripts of the studies that are deemed to run on this instance will use this information to tailor some choices to the specific DAP and data source

INSTANCE - This table displays the list of the tables and columns of the origin data dictionary that are mapped to the instance of the CDM, together with date of last update (both in terms of when the data was accessed by the DAPs, and when the data was actually recorded and can be considered complete). This is to be used, together with a machine-readable version of the ETL, to match the inclusion of the study population and the creation of the study variables to the actual data loaded in the CDM instance. The list is restricted to tables and columns of the origin data dictionary that are included in the current ETL document.

PRODUCTS - This table collects the information associated to each marketed product that may have been prescribed, dispensed or administered to a patient. It contains one row per product

PERSON – contains records of persons that are to enter analysis of this instance of the CDM, and stable data on those persons: date of birth, sex, date of death, ethnicity.

OBSERVATION_PERIODS – contains information on the period of follow-up period per person with multiple observation periods per person possible.

PERSON_RELATIONSHIP - contains identifiers for mother-infant pairs and data on methodology used to link each pair.

MEDICINES – contains data on drug prescriptions, dispensings or administrations occurred during routine healthcare

EVENTS – contains diagnoses, symptoms and signs ('events') observed during routine healthcare, such a hospital admission, a primary care or specialist visit, or other.

PROCEDURES – contains records of procedures administered during routine healthcare. Can be a surgery, or a diagnostic procedure, a rehabilitation procedure, a therapeutic procedure.

MEDICAL_OBSERVATIONS - contains records of medical observations, e.g. clinical measurements, tests.

SURVEY_ID – contains identifiers for persons recorded in surveys captured in the SURVEY_OBSERVATIONS table.

SURVEY_OBSERVATIONS – contains data collected to record data related to an event or episode (i.e. a medical birth registry)

Low level CDM local

Practice details

Patient details

Consultations

Staff

Clinical procedures

Clinical details

Therapy

Referral

Tests

Immunisations

CPRD Data Model
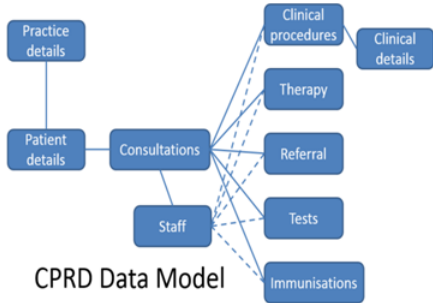
Local Transformation of structure to CDM

Standardized metadata
Data Source Name
Data Access Provider
Date Draw Down
Date Last Update
Link Method
Provenances
sPrescrORDisp
sIndication
sDiary
sEUROCAT
sSpontaneousReport
sObservationPeriods
sDeath
sSchoolRecords
sVaccine Records

Person
Data Source Name
PatientID
DOB
Sex At Birth
Ethnicity

Observation Periods
PatientID
StartDate
EndDate
Provenance

DrugExposure
PatientID
Date
ATC
Brand
Amount Prescribed
Amont Dispensed
Amount Units
Strength
Route
UnitsDay
DDDvalue
ProductCode
Dose Recorded
Vactype
Dose Vac
Indication
IndicationType
IndicationDesc
sPrescrORDisp
Provenance
Prescriber

MotherChild
MPatientID
CPatientID
InfantData
Provenance

Death
PatientID
Date
CauseOfDeath
CodeType
CodeDesc
Provenance

Event
PatientID
Date
Code
CodeType
CodeDesc
Provenance
EncounterCode

measurements
PatientID
Date
Code
CodeType
CodeDesc
MeasurementResult
ResultUnits
Provenance

Encounter
PatientID
Date
VisitType
PhysicianType
DurationVisit

Data check and transformation scripts in R Run locally

Analysis files on platform

ANNEX IV: CODE LISTS

Indications

Table IV.1   Epilepsy

Coding system	Code	Code name
ICD10	G41	Status epilepticus
ICD10	G41.9	Status epilepticus, unspecified
ICD10	G41.8	Other status epilepticus
ICD10	G40.2	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures
ICD10	G40.0	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset
ICD10	G41.1	Petit mal status epilepticus
ICD10	G40.3	Generalized idiopathic epilepsy and epileptic syndromes
ICD10	G40.5	Special epileptic syndromes
ICD10	F80.3	Acquired aphasia with epilepsy [Landau-Kleffner]
ICD10	G41.2	Complex partial status epilepticus
ICD10	G40.8	Other epilepsy
ICD10	G40	Epilepsy
ICD10	G40.9	Epilepsy, unspecified
ICD10	G40.6	Grand mal seizures, unspecified (with or without petit mal)
ICD10	G41.0	Grand mal status epilepticus
ICD10CM	G40.8	Other epilepsy and recurrent seizures
ICD10CM	G40.209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, not intractable, without status epilepticus
ICD10CM	G40.219	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, without status epilepticus
ICD10CM	G40.211	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures, intractable, with status epilepticus
ICD10CM	G40.4	Epilepsy with grand mal seizures on awakening
ICD10CM	G40.20	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures without intractability
ICD10CM	G40.2	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures
ICD10CM	G40.209	Localization-related (focal) (partial) symptomatic epilepsy and epileptic syndromes with complex partial seizures NOS
ICD10CM	G40.5	Epileptic seizures related to external causes
ICD10CM	G40.509	Epileptic seizures related to external causes, NOS
ICD10CM	G40.501	Epileptic seizures related to external causes, not intractable, with status epilepticus
ICD10CM	G40.50	Epileptic seizures related to external causes, not intractable
ICD10CM	G40.909	Epilepsy, unspecified, not intractable, without status epilepticus
ICD10CM	G40.901	Epilepsy, unspecified, not intractable, with status epilepticus
ICD10CM	G40.919	Epilepsy, unspecified, intractable, without status epilepticus

ICD10CM	G40.911	Epilepsy, unspecified, intractable, with status epilepticus
ICD10CM	G40.0	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset
ICD10CM	G40.009	Localization-related (focal) (partial) idiopathic epilepsy and epileptic syndromes with seizures of localized onset NOS
ICD10CM	G40.5	Epileptic seizures related to drugs
ICD10CM	G40.5	Epileptic seizures related to stress
ICD10CM	G40.90	Epilepsy, unspecified, not intractable
ICD10CM	G40.1	Epilepsia partialis continua [Kozhevnikof]
ICD10CM	G40.90	Epilepsy, unspecified, without intractability
ICD10CM	G40.91	Epilepsy, unspecified, intractable
ICD10CM	G40.91	Intractable seizure disorder NOS
ICD10CM	G40.3	Generalized idiopathic epilepsy and epileptic syndromes
ICD10CM	G40.309	Generalized idiopathic epilepsy and epileptic syndromes NOS
ICD10CM	G40.909	Recurrent seizures NOS
ICD10CM	G40.81	Lennox-Gastaut syndrome
ICD10CM	G40.82	Salaam attacks
ICD10CM	G40.8	Landau-Kleffner syndrome
ICD10CM	G40.89	Other seizures
ICD10CM	G40.80	Other epilepsy
ICD10CM	G40.802	Other epilepsy NOS
ICD10CM	R56.9	Unspecified convulsions
ICD10CM	G40.9	Epilepsy, unspecified
ICD10CM	G40.909	Epilepsy NOS
ICD10CM	G40.4	Grand mal seizure NOS
ICD10CM	R56.9	Convulsion disorder
ICD10CM	G40	Epilepsy and recurrent seizures
ICD9CM	345.8	Other forms of epilepsy and recurrent seizures
ICD9CM	345.5	Localization-related (focal) (partial) epilepsy and epileptic syndromes with simple partial seizures
ICD9CM	345.41	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, with intractable epilepsy
ICD9CM	345.40	Localization-related (focal) (partial) epilepsy and epileptic syndromes with complex partial seizures, without mention of intractable epilepsy
ICD9CM	345.0	Generalized nonconvulsive epilepsy
ICD9CM	345.11	Generalized convulsive epilepsy, with intractable epilepsy
ICD9CM	345.10	Generalized convulsive epilepsy, without mention of intractable epilepsy
ICD9CM	345.1	Generalized convulsive epilepsy
ICD9CM	345.2	Petit mal status
ICD9CM	345.7	Epilepsia partialis continua
ICD9CM	780.3	Convulsions
ICD9CM	345.9	Epilepsy, unspecified
ICD9CM	345.3	Grand mal status
ICD9CM	345	Epilepsy and recurrent seizures
ICPC1	N88	Epilepsy all types
ICPC2P	N88004	Status epilepticus;tonic-cloni
ICPC2P	N88015	Seizure;atonic
ICPC2P	N88010	Seizure;focal;complex partial
ICPC2P	N88012	Seizure;tonic

ICPC2P	N88008	Epilepsy;grand mal
ICPC2P	N88005	Epilepsy;temporal lobe
ICPC2P	N88002	Status epilepticus;Petit mal
ICPC2P	N88009	Seizure;focal;simple partial
ICPC2P	N88014	Seizure;myoclonic
ICPC2P	N07001	Convulsions
ICPC2P	N07002	Fit(s)
ICPC2P	N07003	Seizure
ICPC2P	N88003	Seizure;epileptic
ICPC2P	N88006	Epilepsy
ICPC2P	N88011	Seizure;tonic-clonic
ICPC2P	N88001	Status epilepticus;Grand mal
RCD	Fyu59	[X]Status epilepticus, unspec
RCD	X007B	Status epilepticus
RCD	Fyu52	[X]Other status epilepticus
RCD	X006M	Epilepsy with grand mal seizures on awakening
RCD	F250.	Generalised non-convuls epilep
RCD	F250z	Generalised non-convulsive epilepsy NOS
RCD	X75ZD	Atonic seizure
RCD	X75ZA	Tonic seizure
RCD	F2543	Mesiobasal limbic epilepsy
RCD	F2544	Epileptic automatism
RCD	X75Yv	Complex partial seizure with automatisms
RCD	F2510	Grand mal epilepsy
RCD	XM03h	Tonic-clonic convulsion
RCD	F2542	Psychosensory epilepsy
RCD	F2510	Generalised epilepsy
RCD	F2514	Epileptic seizures - tonic
RCD	F2540	Temporal lobe epilepsy
RCD	F251y	General.convuls.epilepsy OS
RCD	F254.	Partial epilep.-consc.impaired
RCD	F254z	Partial epil.-consc.impair.NOS
RCD	F25y2	Localization-related(focal)(partial)idiopathic epilepsy and epileptic syndromes with seizures of localised onset
RCD	F2512	Epileptic seizures - clonic
RCD	F251.	Generalised convulsive epilep.
RCD	F251z	General.convuls.epilepsy NOS
RCD	F2503	Epileptic seizures - akinetic
RCD	F252.	Non-convulsive status epilepticus with impaired consciousness
RCD	F2502	Epileptic seizures - atonic
RCD	X006G	Idiopathic generalised epilepsy
RCD	X006Q	Lennox-Gastaut syndrome
RCD	X50Er	Lennox-Gastat syndrome
RCD	F256.	Blitz-Nick-salaam attacks
RCD	X006o	Acquired epileptic aphasia
RCD	F255y	Other specified partial epilepsy without mention of impairment of consciousness
RCD	F2553	Part.epilepsy+autonomic sympt.

RCD	F255.	Partial epilepsy-conscious OK
RCD	F255z	Partial epilep.-consc.OK NOS
RCD	X75YT	Simple partial seizure, consciousness not impaired
RCD	F2554	Visual reflex epilepsy
RCD	F2552	Somatosensory epilepsy
RCD	F2555	Unilateral epilepsy
RCD	F2551	Epilepsy associated with specific stimuli
RCD	F2513	Epileptic seizures - myoclonic
RCD	X75Z8	Myoclonic seizure
RCD	F257.	Kojevnikov's epilepsy
RCD	X007F	Motor simple partial status
RCD	X007G	Complex partial status epilepticus
RCD	F25y.	Other forms of epilepsy
RCD	F25yz	Other forms of epilepsy NOS
RCD	Fyu51	[X]Other epilepsy
RCD	R003.	[D]Convulsions
RCD	R0032	[D]Fit
RCD	R003z	[D]Convulsion NOS
RCD	XaDbE	Fit - convulsion
RCD	XaEHz	Seizure
RCD	XaEI2	Fits - convulsions
RCD	F25..	Epilepsy
RCD	X75Z0	EF - Epileptic fit
RCD	XaEIj	Epileptic seizure
RCD	XE15a	Epilepsy NOS
RCD	XaBM2	Grand mal seizure
RCD	XM03h	Tonic-clonic seizure
RCD	F1320	Essential myoclonus
RCD	XE15Y	Convulsive status epilepticus

*RCD: Read V3

Table IV.2   Bipolar disorder

Coding system	Code	Code name
ICD10	F30.1	Mania without psychotic symptoms
ICD10	F30.2	Mania with psychotic symptoms
ICD10	F31	Bipolar affective disorder
ICD10	F31.9	Bipolar affective disorder, unspecified
ICD10	F31.8	Other bipolar affective disorders
ICD10	F31.6	Bipolar affective disorder, current episode mixed
ICD10	F31.0	Bipolar affective disorder, current episode hypomanic
ICD10	F31.3	Bipolar affective disorder, current episode mild or moderate depression
ICD10	F31.4	Bipolar affective disorder, current episode severe depression without psychotic symptoms
ICD10	F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms
ICD10	F31.2	Bipolar affective disorder, current episode manic with psychotic symptoms

ICD10	F31.5	Bipolar affective disorder, current episode severe depression with psychotic symptoms
ICD10	F34.0	Cyclothymia
ICD10	F30.0	Hypomania
ICD10	F30	Manic episode
ICD10	F30.9	Manic episode, unspecified
ICD10	F30	Manic episode
ICD10	F30.9	Manic episode, unspecified
ICD10	F31.1	Bipolar affective disorder, current episode manic without psychotic symptoms
ICD10CM	F30	bipolar disorder, single manic episode
ICD10CM	F31.73	Bipolar disorder, in partial remission, most recent episode manic
ICD10CM	F39	Affective psychosis NOS
ICD10CM	F31	Bipolar disorder
ICD10CM	F31.9	Bipolar disorder, unspecified
ICD10CM	F31.8	Other bipolar disorders
ICD10CM	F31.89	Other bipolar disorder
ICD10CM	F31.3	Bipolar disorder, current episode depressed, mild or moderate severity
ICD10CM	F31.30	Bipolar disorder, current episode depressed, mild or moderate severity, unspecified
ICD10CM	F31.1	Bipolar disorder, current episode manic without psychotic features
ICD10CM	F31.10	Bipolar disorder, current episode manic without psychotic features, unspecified
ICD10CM	F31.6	Bipolar disorder, current episode mixed
ICD10CM	F31.60	Bipolar disorder, current episode mixed, unspecified
ICD10CM	F31.5	Bipolar disorder, current episode depressed, severe, with psychotic features
ICD10CM	F31.4	Bipolar disorder, current episode depressed, severe, without psychotic features
ICD10CM	F31.2	Bipolar disorder, current episode manic severe with psychotic features
ICD10CM	F31.7	Bipolar disorder, currently in remission
ICD10CM	F31.0	Bipolar disorder, current episode hypomanic
ICD10CM	F34.0	Cyclothymic disorder
ICD10CM	F31.81	Bipolar II disorder
ICD10CM	F30.8	Hypomania
ICD10CM	F30.9	Mania NOS
ICD10CM	F31.89	Recurrent manic episodes NOS
ICD10CM	F30	Manic episode
ICD10CM	F30.9	Manic episode, unspecified
ICD10CM	F30	Manic episode
ICD10CM	F30.9	Manic episode, unspecified
ICD10CM	F30	mixed affective episode
ICD9CM	296.60	Bipolar I disorder, most recent episode (or current) mixed, unspecified
ICD9CM	296.80	Bipolar disorder, unspecified
ICD9CM	296.89	Other bipolar disorders
ICD9CM	296.54	Bipolar I disorder, most recent episode (or current) depressed, severe, specified as with psychotic behavior
ICD9CM	296.44	Bipolar I disorder, most recent episode (or current) manic, severe, specified as with psychotic behavior

ICD9CM	296.63	Bipolar I disorder, most recent episode (or current) mixed, severe, without mention of psychotic behavior
ICD9CM	296.64	Bipolar I disorder, most recent episode (or current) mixed, severe, specified as with psychotic behavior
ICD9CM	301.1	Affective personality disorder
ICD9CM	301.10	Affective personality disorder, unspecified
ICD9CM	301.13	Cyclothymic disorder
ICD9CM	296.40	Bipolar I disorder, most recent episode (or current) manic, unspecified
ICD9CM	296.81	Atypical manic disorder
ICD9CM	296.1	Manic disorder, recurrent episode
ICD9CM	296.40	Bipolar I disorder, most recent episode (or current) manic, unspecified
ICPC1	P73	Affective psychosis
ICPC2P	P73011	Psychosis;affective
ICPC2P	P73002	Depression;manic
ICPC2P	P73004	Disorder;bipolar
ICPC2P	P73007	Manic depressive
ICPC2P	P73012	Psychosis;manic depressive
ICPC2P	P73008	Hypomania
ICPC2P	P73009	Mania
RCD	Eu301	[X]Mania without psychotic sym
RCD	XE1ZV	[X]Mania with psychotic symptoms
RCD	E11z0	Unspecif.affective psych.NOS
RCD	E117.	Unspec bipolar affect disord
RCD	E1170	Unspecified bipolar affective
RCD	E117z	Unspecif.bipolar affective NOS
RCD	Eu31z	[X]Bipolar affective disorder, unspecified
RCD	X00SM	Bipolar disorder
RCD	XE1ZX	[X]Oth bipolar affectve disord
RCD	E116.	Mixed bipolar affective disord
RCD	E116z	Mixed bipolar affective disorder, NOS
RCD	Eu316	Bipolar affective disorder , current episode mixed
RCD	Eu310	Bipolar affective disorder, current episode hypomanic
RCD	Eu313	[X]Bipol aff mild/mod depress
RCD	Eu314	[X]Bipol AD,cur sev dep,no psy
RCD	Eu311	[X]Bipol aff, manic no psychos
RCD	Eu312	[X]Bipol affect manic+psychos
RCD	E1172	Unsp.bipolar affect.-moderate
RCD	E1171	Unsp.bipolar affective-mild
RCD	E1174	Unsp.bipol.affect.-severe+psyc
RCD	E1173	Unsp.bipolar affect.-severe
RCD	E1175	Unsp.bipol.affect.-part remiss
RCD	E11y3	Other mixed manic-depres psych
RCD	E11y0	Unspecified manic-depressive psychoses
RCD	E114.	Bipolar affective disorder, current episode manic
RCD	E115.	Bipolar affective disorder, current episode depression
RCD	E2110	Affective personality dis.unsp
RCD	E2113	Cyclothymia
RCD	E211z	Affective personality dis. NOS

RCD	Xa3ZM	Tends to be unstable in affect
RCD	E11y1	Atypical manic disorder
RCD	X00SN	Bipolar II disorder
RCD	X00SL	Hypomania
RCD	X00SJ	Mania
RCD	E111.	Recurrent manic episodes
RCD	E1110	Recurrent manic episodes, unspecified
RCD	E111z	Recurrent manic episode NOS
RCD	XE1ZW	[X]Manic episode, unspecified
RCD	XE1ZW	[X]Manic episode, unspecified
RCD	Eu311	[X]Bipol aff, manic no psychos

Table IV.3   Migraine

Coding system	Code	Code name
ICD10	G43.1	Migraine with aura [classical migraine]
ICD10	G43.3	Complicated migraine
ICD10	G43	Migraine
ICD10	G43.9	Migraine, unspecified
ICD10	G43.0	Migraine without aura [common migraine]
ICD10	G43.8	Other migraine
ICD10	G43.2	Status migrainosus
ICD10CM	G43.1	Retinal migraine
ICD10CM	G43.11	Migraine with aura, intractable
ICD10CM	G43.81	Other migraine, intractable
ICD10CM	G43.111	Migraine with aura, intractable, with status migrainosus
ICD10CM	G43.119	Migraine with aura, intractable, without status migrainosus
ICD10CM	G43.1	Migraine preceded or accompanied by transient focal neurological phenomena
ICD10CM	G43.109	Migraine with aura NOS
ICD10CM	G43.1	Classical migraine
ICD10CM	G43.1	Migraine with prolonged aura
ICD10CM	G43	Migraine
ICD10CM	G43.9	Migraine, unspecified
ICD10CM	G43.909	Migraine NOS
ICD10CM	G43.0	Common migraine
ICD10CM	G43.009	Migraine without aura NOS
ICD10CM	G43.8	Other migraine
ICD10CM	G43.4	Hemiplegic migraine
ICD10CM	G43.409	Hemiplegic migraine NOS
ICD10CM	G43.1	Basilar migraine
ICD10CM	G43.7	Chronic migraine without aura
ICD10CM	G43.709	Chronic migraine without aura NOS
ICD10CM	G44.00	Lower half migraine
ICD10CM	G43.829	Menstrual migraine NOS
ICD10CM	G43.91	Migraine, unspecified, intractable
ICD10CM	G43.90	Migraine, unspecified, not intractable

ICD10CM	G43.1	Migraine equivalents
ICD10CM	G43.B	Ophthalmoplegic migraine
ICD10CM	G43.6	Persistent migraine aura with cerebral infarction
ICD10CM	G43.5	Persistent migraine aura without cerebral infarction
ICD10CM	G43.509	Persistent migraine aura NOS
ICD10CM	G43.901	Status migrainosus NOS
ICD10CM	G43.7	Transformed migraine
ICD9CM	346.03	Migraine with aura, with intractable migraine, so stated, with status migrainosus
ICD9CM	346.02	Migraine with aura, without mention of intractable migraine with status migrainosus
ICD9CM	346.01	Migraine with aura, with intractable migraine, so stated, without mention of status migrainosus
ICD9CM	346.00	Migraine with aura, without mention of intractable migraine without mention of status migrainosus
ICD9CM	346.0	Migraine with aura
ICD9CM	346	Migraine
ICD9CM	346.9	Migraine, unspecified
ICD9CM	346.1	Migraine without aura
ICD9CM	346.8	Other forms of migraine
ICD9CM	346.3	Hemiplegic migraine
ICD9CM	346.7	Chronic migraine without aura
ICD9CM	346.4	Menstrual migraine
ICD9CM	346.93	Migraine, unspecified, with intractable migraine, so stated, with status migrainosus
ICD9CM	346.91	Migraine, unspecified, with intractable migraine, so stated, without mention of status migrainosus
ICD9CM	346.92	Migraine, unspecified, without mention of intractable migraine with status migrainosus
ICD9CM	346.90	Migraine, unspecified, without mention of intractable migraine without mention of status migrainosus
ICD9CM	346.6	Persistent migraine aura with cerebral infarction
ICD9CM	346.5	Persistent migraine aura without cerebral infarction
ICD9CM	346.2	Variants of migraine, not elsewhere classified
ICPC1	N89	Migraine
ICPC2P	N89004	Migraine;classical
ICPC2P	N89001	Headache;migraine
ICPC2P	N89003	Migraine
ICPC2P	N89005	Migraine;common
ICPC2P	N89006	Migraine;hemiplegic
ICPC2P	N89010	Migraine;menstrual
ICPC2P	N89007	Migraine;ophthalmic
RCD	X007O	Retinal migraine
RCD	F260.	Migraine with aura
RCD	F260.	Classical migraine
RCD	X007J	Migraine with typical aura
RCD	F26y3	Complicated migraine
RCD	X007K	Migraine with prolonged aura
RCD	F26..	Migraine

RCD	F26z.	Migraine NOS
RCD	F261.	Migraine without aura
RCD	F2610	Atypical migraine
RCD	F261z	Common migraine NOS
RCD	F26y.	Other forms of migraine
RCD	F26yz	Other forms of migraine NOS
RCD	Fyu53	[X]Other migraine
RCD	F26y0	Hemiplegic migraine
RCD	F2623	Basilar migraine
RCD	Xa07H	Migraine - menstrual
RCD	F262.	Migraine variants
RCD	F262z	Migraine variant NOS
RCD	F2624	Ophthalmic migraine
RCD	F26y1	Ophthalmoplegic migraine
RCD	X007R	Status migrainosus

Adverse reactions

Table IV.4   Adverse reactions to valproates: nausea

Coding system	Code	Code name
ICD10	R11	Nausea and vomiting
ICD10CM	R11.0	Nausea
ICD10CM	R11	Nausea and vomiting
ICD10CM	R11.2	Nausea with vomiting, unspecified
ICD9CM	787.0	Nausea and vomiting
ICD9CM	787.01	Nausea with vomiting
ICPC	D09	Nausea
ICPC2P	D09002	Nausea
RCD	198Z.	Nausea NOS
RCD	R0700	[D]Nausea
RCD	X75qw	Nausea
RCD	Xa7ee	Observation of nausea
RCD	R070.	[D]Nausea and vomiting
RCD	R070z	[D]Nausea and vomiting NOS
RCD	Xa1pJ	Nausea and vomiting
RCD	1982.	Nausea present

Table IV.5   Adverse reactions to valproates: tremor

Coding system	Code	Code name
ICD10	R25.1	Tremor, unspecified
ICD10	G25.0	Essential tremor
ICD10CM	R25.1	Tremor, unspecified
ICD10CM	G25.0	Essential tremor
ICD9CM	333.1	Essential and other specified forms of tremor
ICPC2P	N06009	Shaking
ICPC2P	N06014	Tremor

ICPC2P	N08003	Shaking
ICPC2P	N08005	Tremor
ICPC2P	N99033	Benign essential tremor
RCD	R0103	[D]Tremor NOS
RCD	XE0rn	Tremor
RCD	XM0z1	Tremor [D]
RCD	XM1F4	Shaking all over
RCD	F131.	Essential and other specified forms of tremor
RCD	F131z	Essen.+other spec.tremor NOS
RCD	XE0ro	Trembles
RCD	XM1F4	Trembling
RCD	F1310	Essential tremor

Pregnancy testing

Table IV.6   Pregnancy testing

Coding system	Code	Code name
ICD10	Z32.0	Pregnancy, not (yet) confirmed
ICD10	Z32	Pregnancy examination and test
ICD10	Z32.1	Pregnancy confirmed
ICD10CM	Z32.02	Encounter for pregnancy test, result negative
ICD10CM	Z32.01	Encounter for pregnancy test, result positive
ICD10CM	Z32.00	Encounter for pregnancy test, result unknown
ICD10CM	Z32.0	Encounter for pregnancy test
ICD10CM	Z32.00	Encounter for pregnancy test NOS
ICD9CM	V72.40	Pregnancy examination or test, pregnancy unconfirmed
ICD9CM	V72.4	Pregnancy examination or test
ICD9CM	V72.42	Pregnancy examination or test, positive result
ICPC1	W01	Question of pregnancy
ICPC2P	W33002	Test;pregnancy
ICPC2P	W33001	Test;urine;pregnancy
ICPC2P	W35004	Test;urine;pregnancy
ICPC2P	W35003	Test;urine;HCG
ICPC2P	W01001	? Pregnancy
ICPC2P	W60001	Test;result(s);pregnancy
RCD	445Z.	Serum pregnancy test NOS
RCD	4651.	Urine pregnancy test requested
RCD	4653.	Urine pregnancy test equivocal
RCD	4655.	High sensitivity urine pregnancy test
RCD	4453.	Serum pregnancy test positive
RCD	4451.	Serum pregnancy test negative
RCD	X77WY	Pregnancy test
RCD	465..	Urine pregnancy test
RCD	465Z.	Urine pregnancy test NOS
RCD	445..	Serum pregnancy test (B-HCG)
RCD	ZV724	[V]Pregnancy examination or test, pregnancy unconfirmed
RCD	6219.	Possible pregnancy

RCD	XaBMk	[V]Pregnancy not (yet) confirmed
RCD	XaBMj	[V]Pregnancy examination and test
RCD	ZV222	[V]Pregnancy confirmed
RCD	X76xz	Pregnancy test negative
RCD	X76xv	Pregnancy test observation
RCD	X76xx	Pregnancy test positive

Contraception or procedures causing infertility

Table IV.7   Female Sterilization

ICD10	Z30.2	Sterilization
ICD10CM	Z30.2	Encounter for sterilization
ICD10CM	Z98.51	Tubal ligation status
ICD9CM	V25.2	Sterilization
ICD9CM	66.51	Removal of both fallopian tubes at same operative episode
ICD9CM	V26.51	Tubal ligation status
ICPC2P	X52013	Salpingectomy
ICPC2P	W52002	Tubal ligation;procedure
RCD	Xa3vr	Salpingectomy NOS
RCD	Xa8Pb	Salpingectomy
RCD	ZV252	[V]Admission for sterilisation
RCD	X403g	Laparoscopic tubal occlusion
RCD	X403f	TL - Tubal ligation

Table IV.8   Hysterectomy

Coding system	Code	Code name
ICD10	N99.3	Prolapse of vaginal vault after hysterectomy
ICD10CM	N99.3	Prolapse of vaginal vault after hysterectomy
ICD10CM	Z90.711	Acquired absence of uterus with remaining cervical stump
ICD10CM	Z90.711	Status post partial hysterectomy with remaining cervical stump
ICD10CM	Z90.71	Acquired absence of cervix and uterus
ICD10CM	Z90.710	Status post total hysterectomy
ICD9CM	618.5	Prolapse of vaginal vault after hysterectomy
ICD9CM	V88.02	Acquired absence of uterus with remaining cervical stump
ICD9CM	V88.0	Acquired absence of cervix and uterus
ICD9CM	68.4	Total abdominal hysterectomy
ICD9CM	68.49	Other and unspecified total abdominal hysterectomy
ICD9CM	68.41	Laparoscopic total abdominal hysterectomy
ICD9CM	68.6	Radical abdominal hysterectomy
ICD9CM	68.5	Vaginal hysterectomy
ICD9CM	68.7	Radical vaginal hysterectomy
ICD9CM	68.51	Laparoscopically assisted vaginal hysterectomy (LAVH)
ICD9CM	68.59	Other and unspecified vaginal hysterectomy
ICD9CM	68.3	Subtotal abdominal hysterectomy
ICPC2P	X52018	Hysterectomy

ICPC2P	X52010	Hysterectomy;abdomin;total
ICPC2P	X52011	Hysterectomy;vaginal
ICPC2P	X52009	Hysterectomy;abdomin;subtotal
RCD	K515.	Post-hysterectomy vaginal vault prolapse
RCD	X403B	Hysterectomy
RCD	Xa3ve	Hysterectomy NOS
RCD	XE06Z	Total abdominal hysterectomy
RCD	XE06a	Total abdominal hysterectomy and bilateral salpingo-oophorectomy
RCD	Xa9gY	Total abdominal hysterect NEC
RCD	XaBEI	Radical abdominal hysterectomy
RCD	7E05z	Vaginal excision of uterus NOS
RCD	XE06b	Vaginal hysterectomy
RCD	7E050	Radical vaginal hysterectomy
RCD	XE06c	Vaginal hysterectomy NEC
RCD	XE06d	Other specified vaginal excision of uterus
RCD	X403C	Laparoscopy assisted vaginal hysterectomy
RCD	7E044	Subtotal abdominal hysterectomy
RCD	7E04z	Abdominal excision of uterus NOS
RCD	XE06Y	Abdominal hysterectomy
RCD	XM1HX	Hysterectomy NEC
RCD	X403D	Laparoscopic hysterectomy
RCD	7E046	Radical hysterectomy
RCD	7F1A0	Caesarean hysterectomy

Table IV.9   Intrauterine device

Coding system	Code	Code name
ICD10	Z30.1	Insertion of (intrauterine) contraceptive device
ICD10	Z97.5	Presence of (intrauterine) contraceptive device
ICD10CM	Z97.5	Presence of (intrauterine) contraceptive device
ICD9CM	69.7	Insertion of intrauterine contraceptive device
ICD9CM	V45.51	Presence of intrauterine contraceptive device
ICPC1	W12	Family planning/IUD
ICPC2P	W12003	Contraception;IUD
ICPC2P	W12004	Insertion;IUCD
RCD	ZV254	[V]IUCD reinsertion
RCD	615G.	IUD in situ
RCD	XaDbJ	IUD contraception
RCD	6151.	Intrauterine contraceptive device fitted
RCD	7E090	Introduction of intrauterine contraceptive device
RCD	ZV251	[V]Coil insertion
RCD	6153.	Intrauterine contraceptive device re-fitted
RCD	615F.	IUD check
RCD	XM15M	Intrauterine device check
RCD	ZV455	[V]Intraut.contrac.dev.present
RCD	XaDbF	Intrauterine contraception

ANNEX V: NATIONAL DATES OF PPP IMPLEMENTATION

The following information was collected and compiled by EMA (June 2019)

Table V.1 Implementation in Denmark

Country: Denmark		
Measure implemented (please tick)	**Date of implementation (DD/MM/YYYY)**	**Implementation delayed for product(s)**
☐ Updated SmPC	The first updated SmPC was implemented on 16-07-2018.	Orfiril Orfiril Long Orfiril Retard
☐ Updated PIL with boxed warning and Quick Response (QR) code	The first variation to update the PL was approved on 16-07-2019. From this date, the changes in the PL including QR code must be implemented in the actual packaging within 6 month.	Orfiril Orfiril Long Orfiril Retard
☐ Visual reminder outer packaging	The first variation to update the labelling was approved on 16-07-2018. From this date, the changes to the labelling must be implemented on the actual packaging within 6 month. In Denmark the boxed warning is considered the visual reminder. No pictogram is allowed.	Orfiril Orfiril Long Orfiril Retard
☐ Patient reminder card	11-10-2018	
☐ Healthcare professional guide	11-10-2018	
Patient guide	11-10-2018	
☐ Risk acknowledgement form with prescriber and patient/carer checklist	11-10-2018	
☐ DHCP	11-10-2018	
☐ Any other measures:	N/A	

Table V.2 Implementation in Italy

Country: ITALY		
Measure implemented (please tick)	**Date of implementation (DD/MM/YYYY)**	**Implementation delayed for product(s)**
☒ Updated SmPC	02/10/2018	
☒ Updated PIL with boxed warning and Quick Response (QR) code	02/10/2018	
☒ Visual reminder outer packaging	02/10/2018	
☒ Patient reminder card	08/08/2018	
☒ Healthcare professional guide	08/08/2018	
☒ Patient guide	08/08/2018	
☒ Risk acknowledgement form with prescriber and patient/carer checklist	08/08/2018	
☒ DHCP	08/08/2018	
☒ Any other measures: The following document are published on AIFA website: • Patient reminder card • Healthcare professional guide • Patient guide • Risk acknowledgement form with prescriber and patient/carer checklist • DHCP	08/08/2018	

Table V.3 Implementation in The Netherlands

Country: Netherlands		
Measure implemented (please tick)	**Date of implementation** (DD/MM/YYYY)	**Implementation delayed for product(s)**
☒ Updated SmPC	10/08/2018	None.
☒ Updated PIL with boxed warning and Quick Response (QR) code	10/08/2018	None.
☒ Visual reminder outer packaging	12-12-2018	Note: we are not aware if these are also already available in the market.
☒ Patient reminder card	12-12-2018	Note: the patient card has been implemented as a separate card and is not yet attached at the package. Discussion about this is ongoing with all MAHs to discuss feasibility and time periods.
☒ Healthcare professional guide	12-12-2018	None, it is joint material applicable for all MAHs
☒ Patient guide	12-12-2018	None, it is joint material applicable for all MAHs
☒ Risk acknowledgement form with prescriber and patient/carer checklist	12-12-2018	None, it is joint material applicable for all MAHs
☒ DHCP	12-12-2018	None, it is joint material applicable for all MAHs

Table V.4 Implementation in Spain

Country: Spain		
Measure implemented (please tick)	**Date of implementation** (DD/MM/YYYY)	**Implementation delayed for product(s)**
×☐ Updated SmPC	December 2018 (DepakineNovember 2018)	
×☐ Updated PIL with boxed warning and Quick Response (QR) code	December 2018 (DepakineNovember 2018)	
×☐ Visual reminder outer packaging	31/7/2018	
×☐ Patient reminder card	31/7/2018	
×☐ Healthcare professional guide	31/7/2018	
×☐ Patient guide	31/7/2018	
×☐ Risk acknowledgement form with prescriber and patient/carer checklist	31/7/2018	
×☐ DHCP	24/7/2018	

Table V.5 Implementation in the United Kingdom

Country: UK		
Measure implemented (please tick)	**Date of implementation** (DD/MM/YYYY)	**Implementation delayed for product(s)**
☒ Updated SmPC	30/4/2018: SmPC changes approved for brand leader (Sanofi) valproate medicines	Other products' SmPCs updated by November 2018.
☒ Updated PIL with boxed warning and Quick Response (QR) code	<u>Brand leader (Sanofi) valproate medicines</u> - 30/4/2018: PIL changes approved, including boxed warning - 8/11/2018: approved introduction of QR code on PIL	
☒ Visual reminder outer packaging	<u>Brand leader (Sanofi) valproate medicines</u> 7/3/2018: approved pictogram and carton warning	
☒ Patient reminder card	- May 2018: available online for download - July 2018: First DHPC letters with packs of PPP materials, including patient card, sent by Sanofi to pharmacists - Detachable patient card (new outer packaging): approved in February 2019	
☒ Healthcare professional guide	- May 2018: available online for download - July 2018: First DHPC letters with packs of PPP - materials sent by Sanofi to pharmacists and HCPs	
☒ Patient guide	- May 2018: available online for download - July 2018: First DHPC letters with packs of PPP materials sent by Sanofi to pharmacists - and HCPs	
☒ Risk acknowledgement form with prescriber and patient/carer checklist	- May 2018: available online for download - July 2018: First DHPC letters with packs of PPP materials, including risk acknowledgement form, sent by Sanofi to HCPs - April 2019: Updated risk - acknowledgement form available online	
☒ DHCP	- June 2018: available online for download (eMC website) - July 2018: First DHPC letters with packs of PPP materials sent by Sanofi to pharmacists - and HCPs	