PASS information

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
EU PAS register number	EUPAS8412
Active substance	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, anti-androgens and oestrogens
Medicinal product	Diane®-35 and its generics
Product reference	*Reference number(s) of centrally authorised products and/or, if possible, of nationally authorised products subject to the study*
Procedure number	Referral: EMEA/H/A-107i/1357
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Joint PASS	Yes
Research question and objectives	The study objectives are to characterize new users of CPA/EE in 2011/2012 and in 2014 according to demographics, treatment characteristics, previous diagnosis of acne, hirsutism or other hyperandrogenic conditions, previous acne treatment and (concomitant) use of hormonal contraceptives. A secondary objective is to compare patient and treatment characteristics between January 1, 2011 and December 31, 2012 and January 1, 2014 and December 31, 2014. An additional objective, added in 2017, is to study demographics and concomitant use of hormonal contraceptives in 2015, 2016 and 2017 as well.
Country(-ies) of study	The Netherlands, United Kingdom, Italy
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The study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Throughout this document, symbols indicating proprietary names (®, TM) may not be displayed. Hence, the appearance of product names without these symbols does not imply that these names are not protected.

1. Table of contents

2. List of abbreviations

ANSM	National Agency for the Safety of Medicine and Health Products
ATC code	Anatomical Therapeutic Chemical code
CEIFE	Centro Español de Investigación Farmacoepidemiológica
CI	Confidence Interval
CMDh	The Coordination Group for Mutual Recognition and Decentralised Procedures – Human
CPA/EE	Cyproterone/ethinylestradiol
DUS	Drug utilization study
EMA	European Medicines Agency
GP	General Practitioner
HC	Hormonal contraceptives
HSD	Health Search Database
ICD-10	International Classification of Diseases 10th Edition
ICD-9(-CM)	International Classification of Diseases 9th Edition (Clinical Modification)
ICPC	International Classification of Primary Care
IQR	Interquartile Range
LMR	Landelijke Medische Registratie - Dutch Medical Register
MAH	Marketing Authorization Holder
PASS	Post-Authorization Safety Study
PCOS	Polycystic ovary syndrome
PHARMO	PHARMO Database Network
PRAC	European Medicines Agency's Pharmacovigilance Risk Assessment Committee
SD	Standard Deviation
THIN	The Health Improvement Network
UK	United Kingdom
WHO	World Health Organization
IQR	Interquartile Range

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4. Abstract

Title: Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy.

Rationale and background: A drug utilization study (DUS) on the use of cyproterone/ethinylestradiol (CPA/EE) in three European countries will be performed. Initiated by concerns from the French medicines agency about the safety risks of CPA/EE, the Pharmacovigilance Risk Assessment Committee (PRAC) conducted a product review and concluded that the benefits of CPA/EE outweigh the risks, provided that several measures are taken to minimise the risk of venous thromboembolism.

Research question and objectives: The study objectives are to characterize new users of CPA/EE between January 1, 2011 and December 31, 2012 and January 1, 2014 and December 31, 2014 according to demographics, treatment characteristics, previous diagnosis of acne, hirsutism or other hyperandrogenic conditions, previous acne treatment and (concomitant) use of hormonal contraceptives. A secondary objective is to compare patient and treatment characteristics between January 1, 2011 and December 31, 2012 and January 1, 2014 and December 31, 2014. An additional objective, is to study demographics and concomitant prescription of hormonal contraceptives in 2015, 2016 and 2017 as well.

Study design: A cohort study will be performed among new users of CPA/EE identified in three European population-based health care databases from the United Kingdom (UK) (THIN), the Netherlands (PHARMO) and Italy (HSD). The study will be conducted twice: the first run will include new users in 2011/2012 and the second run will include new users in 2014.

Population: The study population will include all female patients registered in the databases receiving CPA/EE in 2011 or 2012 (first run), 2014 (second run) or 2015, 2016 or 2017 (study extension) without a prescription of CPA/EE in the year prior to index date. Only patients with recorded history in the database of ≥ 365 days prior to index date will be included in the study. Patients will be followed from index date to transfer out of the database (end of follow-up available/censoring) or end of the study period.

Variables: The following characteristics will be assessed in the study population:

- Demographic characteristics (age, available history, available follow-up)
- CPA/EE treatment characteristics of the first episode of use (Diane 35 or generic, duration of CPA/EE use, prescriber)
- Acne treatment in the year prior to index date (topicals, systemic preparations and hormonal agents)
- Diagnoses in the year prior to index date (acne, alopecia, contraceptive management, menstrual problems, hirsutism, oligomenorrhoea / amenorrhoea, polycystic ovary syndrome (PCOS), seborrhea)
- Use of hormonal contraceptives before, during or after each episode of CPA/EE use (non-concomitant, potential concomitant, concomitant, no use of hormonal contraceptives). All

administration routes of hormonal contraceptives will be included in the study: pills, intra-uterine devices, implants, injections, rings and patches.

- For the study extension: demographic characteristics as above, duration of CPA/EE use and concomitant use of hormonal contraceptives

Data sources: The study will be conducted in the following databases:

- PHARMO Database Network (PHARMO) – The Netherlands
- The Health Improvement Network (THIN) – United Kingdom
- Health Search Database (HSD) – Italy

Study size: In a preliminary analysis of 2011-2012 about 9000 new users of CPA/EE were observed in the three databases.

Data analysis: Patient, treatment and diagnosis characteristics will be reported descriptively. Categorical data will be presented as counts (n) and proportions (%). Continuous data will be presented as means with standard deviation (SD) and as medians with inter quartile range (IQR) when appropriate. Prescriptions of CPA/EE and hormonal contraceptives between index date – 365 days and end of follow-up will be converted into treatment episodes of uninterrupted use. In case of an interruption between two prescriptions, use of the agent will be considered interrupted and the treatment episode ends, i.e. no gap is allowed between two prescriptions. Patients may have several treatment episodes after treatment onset. Episodes of the two classes (CPA/EE and hormonal contraceptives) may overlap, indicating concomitant drug use when there is complete overlap. Partial overlap will be defined as 'potential concomitant use'. Results will be presented for the 2011/2012 users together and stratified by year of diagnosis.

Milestones: The data of 2014 for the three databases (THIN, PHARMO, HSD) will become available mid-2015. Considering a time period of ca. 6 months for analysis of the data and report writing, a final study report is planned for March 2016. Regulatory submission of the study protocol for the database Drug Utilization Study is planned for the third quarter of 2014. An interim report containing 2011/2012 results from the first run will be delivered in Q3 2015.
The data of 2017 for the three databases (THIN, PHARMO, HSD) will become available mid-2018. The study report for the additional obectives will be ready in Q1 2019.

5. Amendments and updates

Table 5.1 Amendments and updates to the Study Protocol

Number	Date	Section of Study Protocol	Amendment or update	Reason

Table 5.1 Amendments and updates to the Study Protocol

Number	Date	Section of Study Protocol	Amendment or update	Reason
1	30 March 2015	9.2 Setting	A prescription of CPA/EE in the year prior to index date was an exclusion criterion. In PHARMO, users were excluded as prevalent also when the prescription was more than one year prior to the index date but expired less than one year before the index date.	Exclusion of these women was more accurate.
2	30 March 2015	9.2 Setting	In the Study Protocol an analysis of 2011/2012 was planned as well as an analysis of 2011 and 2012 separately. In the study report, only the calendar year analysis is presented.	The difference in recruitment periods between the analyses was confusing and the results in the analyses were similar. As the comparison of the 2014 analysis will be with the calendar years cohorts, it was decided to only present these.
3	29 May 2015	9.2 Setting	PHARMO and HSD users who were new users in 2011 as well as in 2012, i.e. were using CPA/EE for a short time in 2011 and re-started after more than 365 days in 2012, were included in both populations. In THIN the 365-day period was applied before the date of study period entry, i.e. before Jan 1, 2011. By definition no users could re-enter in 2012.	At CEIFE standard procedure is to apply the medication-free period to the time before entry date rather than the index date. In practice this leads to only very small differences in numbers of users selected.
4	29 May 2015	9.3 Variables	The index date was included in the assessment of diagnoses of acne and other hyperandrogenic conditions.	Extending the time window up to the index date also included the diagnoses recorded on the date of CPA/EE prescription, i.e. the likely indication of use.
5	19 June 2015	9.3.2 Definition of switching and (potential) concomitant use of CPA/EE and hormonal contraceptives	In THIN, HC episodes were only created after the index date, not before. Overlap between other HC and CPA/EE before index date was assessed examining overlap between HC prescriptions and the first CPA/EE episode.	Different interpretation of the Study Protocol and different local standard programs.

Table 5.1 Amendments and updates to the Study Protocol

Number	Date	Section of Study Protocol	Amendment or update	Reason
6	April 2017	8.2. Additional study objective	Study objectives added are to assess among new users of CPA/EE in 2015, 2016 and 2017: o Patient demographics o (Concomitant) use of hormonal contraceptives o To assess trends in concomitant use over 2011-2017 (excluding 2013)	At the beginning of December 2016, right after the PRAC December meeting, PRAC concluded that the Benefit/Risk balance of Diane-35 and its generics remains unchanged. However, it was requested that Bayer do the the following: • Submission to CA of a follow-up review of available drug utilisation data from electronic healthcare record databases* comparing the patterns of concomitant use over time (Q1 2019) • Update the RMP to include the requested follow-up review of drug utilisation data as a category 3 study, and submission to CA (June 2017). *The MAH is requested to use the same methodology and mode of results presentation as in the previous database DUS, for facilitating the comparison of patterns of use over time. For the same reason, use of the same databases is preferred.

6. Milestones

Regulatory submission of the study protocol for the database Drug Utilization Study is planned for the third quarter of 2014. A progress (interim) report containing 2011/2012 results will be delivered in Q3 2015.

The data of 2014 for the three databases (THIN, PHARMO, HSD) will become available mid-2015. Considering a time period of ca. 6 months for analysis of the data and report writing, a final study report is expected to be available by March 2016. Separate study results for the three partner databases will be compiled in one document. Currently planned dates for deliverables are indicated in Table 6.1.

The data of 2017 for the three databases (THIN, PHARMO, HSD) will become available mid-2018. The study report for the additional obectives will be ready in Q1 2019.

Table 6.1 Planned deliverables

Deliverable	Date
Start of data collection	One month after protocol approval
End of data collection	January 2016
Progress (interim) report to PRAC	Q3 2015
Final report of study results	March 2016
Start of data collection for additional objectives	Q3 2018
End of data collection for additional objectives	Q3 2018
Final report of study results	Q1 2019

7. Rationale and background

Cyproterone acetate (CPA) 2mg, in combination with ethinylestradiol (EE) 35mcg is a medicinal product currently indicated for the treatment of moderate to severe acne and/or for hirsutism in women of reproductive age. Androgen-dependent symptoms such as acne, hirsutism, seborrhea, and alopecia, as well as androgen sensitivity-related symptoms of Polycystic Ovary Syndrome (PCOS) have been considered as potential therapeutic targets for CPA. Due to the mode of action and the dose and regimen, the preparations also act as effective contraceptives. Market authorization was first granted in 1985.

A review of CPA/EE was triggered by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), following its decision to suspend CPA/EE in France within three months in January 2013. The French decision followed a national review of the medicine by ANSM. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed the recommendation of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC), which concluded that the benefits of CPA/EE (cyproterone acetate 2mg / ethinylestradiol 35mcg) outweigh the risks, provided that several measures are taken to minimize the risk of thromboembolism. These medicines should be used solely in the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of reproductive age. Furthermore, CPA/EE should only be used for the treatment of acne when alternative treatments, such as topical therapy and antibiotic treatment, have failed.

Since CPA/EE also acts as a hormonal contraceptive, women should not take this medicine in combination with a hormonal contraceptive. The concomitant use of CPA/EE with a hormonal contraceptive would expose women to a higher hormonal dose and therefore potentially increase the risk of thromboembolism.

During the referral procedure, the risk of thromboembolism occurring with CPA/EE was assessed as low and well known. However, to minimize this risk, the respective MAHs were required to implement further measures in addition to updating the product information, provide educational materials to prescribers and patients highlighting the risks of thromboembolism[1] and to conduct drug utilization and post authorisation safety studies.

This document presents the protocol for a drug utilization study (DUS) on the use of CPA/EE in three European countries. The outline of the study was laid out in the EU Risk Management Plan, Version

1.3 which was finalized in the Variation Worksharing Procedure procedure number NL/H/xxxx/WS/065 on 11 May 2014.

8. Research questions and objectives

8.1 Main study objectives

The main study objectives are to assess among new users of CPA/EE:

- Patient demographics
- Treatment characteristics
- Previous diagnosis of acne, hirsutism or other hyperandrogenic conditions
- Previous acne treatment
- (Concomitant) use of hormonal contraceptives

A secondary objective is:

- to compare patient and treatment characteristics between 2011/2012 and 2014

8.2 Additional objectives

An additional study objectives added are to assess among new users of CPA/EE in 2015, 2016 and 2017:

- Patient demographics
- (Concomitant) use of hormonal contraceptives
- to assess trends in concomitant use over 2011-2017 (excluding 2013)

9. Research methods

9.1 Study design

Retrospective cohort study.

9.2 Setting

The study population will include all individuals registered in the databases receiving CPA/EE (ATC G03HB01) and Gemscript codes (85864998, 86466998, 86925998, 87351998, 90826979, 91068998, 91069998, 94832990, 94913992, 94920998, 95396990, 96577998 and 97520998) between January 1, 2011 and December 31, 2012 (study period for the first run) or January 1, 2014 and December 31, 2014 (study period for the second run). The year 2013 is not included in the identification period, as this is the year in which changes in policies and recommendations for CPA/EE usage have been implemented. The date of receiving the first prescription of CPA/EE in the study period will be defined as the index date.

The annual study periods for the 2017 extension will be between January 1 and December 31 of 2015, 2016 and 2017, respectively.

Exclusion criteria are:

- Men
- <365 days recorded history in the database prior to index date
- Use of CPA/EE in the year prior to the index date, defined by
    - a prescription of CPA/EE in the year prior to index date, or
    - a prescription of CPA/EE in the year prior to entry date (start of the study period or database entry, whichever occurred first) (THIN only, see Table 5.1 deviation #3) or
    - expiration of a prescription of CPA/EE in the year prior to index date (PHARMO only, see Table 5.1 deviation #1)

Patients will be followed from index date to transfer out of the database (end of follow-up available/censoring), end of study period, whichever occurs first. The first run will include an overall analysis (2011-2012) and an analysis by calendar year (2011 and 2012), for which separate recruitments will be performed (i.e. summing patients from the analysis by calendar year 2011 and 2012 may give a higher number than for the overall analysis). In the analysis by calendar year the end of the study period will defined as December 31 of the year of index date (December 31, 2011, December 31, 2012).
For the 2017 study extension an analysis by calender years will be performed..

9.3 Variables

The following demographic characteristics will be assessed in the study population:

- Age at index date (in years, categorized, mean (± SD), median (IQR))
- History available prior to the index date (in years, categorized, mean (± SD), median (IQR))
- Follow-up available after the index date (in months, categorized, mean (± SD), median (IQR))

Prescriptions of CPA/EE from index date until end of follow-up will be converted into treatment episodes of uninterrupted use (see section 9.3.1). For hormonal contraceptives this will be done from one year preceding the index date until end of follow-up. ATC and Gemscript codes of hormonal contraceptives are displayed in Table 16.1 and Table 16.2 of Annex 1.

The following CPA/EE treatment characteristics will be assessed at index date:

- Type of CPA/EE (Diane 35 or generic)
- Prescriber (GP, dermatologist, gynaecologist, other specialist, unknown)

NOTE: Distinction between prescriber is only available in PHARMO. In THIN and HSD all prescriptions come from GPs. There are no prescriptions from specialists, but prescriptions may be started by specialists (not captured) and subsequently continued by the GP.

The following CPA/EE treatment characteristics will be assessed from index date until end of follow-up:

- Number of treatment episodes (categorized, mean (± SD), median (IQR))
- Summed duration of CPA/EE use (in months, categorized, mean (± SD), median (IQR))
- Concomitant use of hormonal contraceptives (concomitant, potential concomitant, non-concomitant or no use of hormonal contraceptives
- Duration of concomitant use of CPA/EE and hormonal contraceptives (≤28 days concomitant use, >28 - 84 days concomitant use or >84 days concomitant use, mean (± SD), median (IQR))
- Duration of potential concomitant use of CPA/EE and hormonal contraceptives (≤28 days potential concomitant use, >28 - 84 days potential concomitant use or >84 days potential concomitant use, mean (± SD), median (IQR))

Prior treatment of acne, according to European treatment guidelines[2], will be assessed in the year prior to the index date (index date – 365 days, excluding index date; for included product names and ATC codes see Table 16.3 and Table 16.4 in Annex 2). Acne treatments will be classified as topicals, systemic preparations and hormonal agents and assessed separately for patients with and without an acne diagnoses in the year prior to index date. Because many of the drugs in the tables are not specific for acne, a pragmatic approach will be taken to select actual acne treatment in the study population: 1) select drugs by ATC or Gemscript code; 2) define dose and route of administration; 3) check with local guidelines for the approved indication of use and only include drugs that are approved for acne (alternative indications may exist). This check with the local guidelines is efficient because only the drugs that are actually used in the study population have to be checked once this data is available. Acne treatments will be further classified to whether it is only approved for acne, or also approved for other indications to allow sensitivity analysis.

Prior diagnoses of hyperandrogenic conditions or medical conditions where EE/progestin combinations are prescribed for frequently will be assessed in the year prior to index date (index date – 365 days, excluding index date; for included codes, see Table 16.5 and Table 16.6):

- Acne
- Alopecia
- Contraceptive management
- Hirsutism
- Menstrual problems
- Oligomenorrhoea/amenorrhoea
- Polycystic ovary syndrome (PCOS)
- Seborrhea

For the 2017 study extension the following will be assessed:.

Demographic characteristics:

- Age at index date (in years, categorized, mean (± SD), median (IQR))
- History available prior to the index date (in years, categorized, mean (± SD), median (IQR))
- Follow-up available after the index date (in months, categorized, mean (± SD), median (IQR))

Concomitant use of hormonal contraceptives:

- Number of CPA/EE treatment episodes (categorized, mean (± SD), median (IQR))
- Summed duration of CPA/EE use (in months, categorized, mean (± SD), median (IQR))
- Concomitant use of hormonal contraceptives (concomitant, potential concomitant, non-concomitant or no use of hormonal contraceptives
- Duration of concomitant use of CPA/EE and hormonal contraceptives (≤28 days concomitant use, >28 - 84 days concomitant use or >84 days concomitant use, mean (± SD), median (IQR))
- Duration of potential concomitant use of CPA/EE and hormonal contraceptives (≤28 days potential concomitant use, >28 - 84 days potential concomitant use or >84 days potential concomitant use, mean (± SD), median (IQR))

9.3.1 Episodes of CPA/EE and hormonal contraceptive use

The duration of each CPA/EE and hormonal contraceptive prescription will include the medication-free days, if applicable. For CPA/EE, which is dosed in cycles of 21 days on medication and a 7-day interval without medication, the duration of one blister pack will thus be 28 days and the duration of a prescription will be the duration of one blister pack * the number of blister packs prescribed (see Figure 9.1). Most (if not all) oral hormonal contraceptives, patches and rings are also dosed in 28-day cycles with variations in the number of medication-free days. For intra-uterine devices, injections and implants the duration will be defined as the duration of effectiveness or until removal of the intra-uterine devices or implant when this is identified in the database. For each hormonal contaceptive the duration of effectiveness will be defined from the label.

Subsequent prescriptions of the same drug will be concatenated if the new prescription date precedes the end date of the previous prescription. The adjusted start date of the new prescription will be the day after the end date of the previous prescription. Subsequently, prescriptions of CPA/EE and hormonal contraceptives between index date – 365 days and end of follow-up will be converted into treatment episodes of uninterrupted use. In case of an interruption between two prescriptions, use of the drug will be considered interrupted and the treatment episode ends, i.e. no gap is allowed between two prescriptions.

Patients may have several treatment episodes of CPA/EE and hormonal contraceptives after treatment onset.

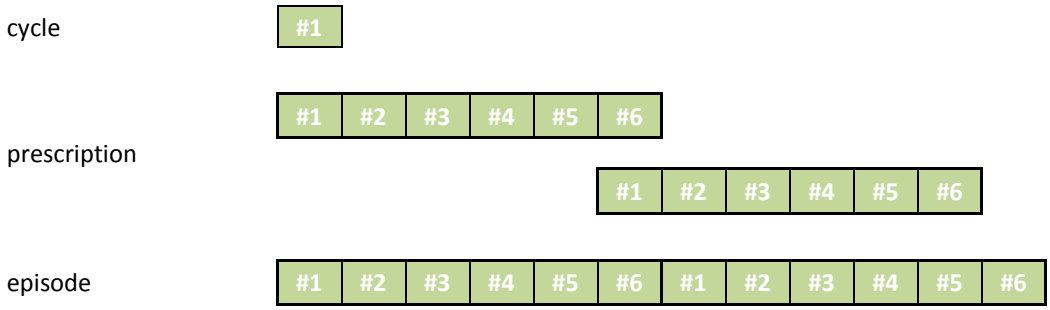

Figure 9.1 Cycles, prescriptions and treatment episodes of CPA/EE and hormonal contraceptives

Each box indicates one cycle, e.g. a blister pack. Subsequent cycles constitute a prescription, and subsequent prescriptions constitute a treatment episode.

9.3.2 Definition of switching and (potential) concomitant use of CPA/EE and hormonal contraceptives

Switching between hormonal contraceptives will be defined as a prescription date of a new hormonal contraceptive preceding the end date of a previous episode of another hormonal contraceptive. As most hormonal contraceptives are given in cycles, the assumption will be that the user will finish a cycle (e.g. the blister pack or patch) of the first hormonal contraceptive before starting a new one. Hence, the adjusted end date of the previous episode will be the end date of the cycle during which the new prescription was observed. The adjusted start date of the new hormonal contraceptive will be the day after the adjusted end date of the previous.
If the previous contraceptive is not given in cycles (e.g. progestogen-only pills, intra-uterine devices, implants) the adjusted end date will be the day before the date of the new prescription and the start date of the new hormonal contraceptive will not be adjusted.

For all episodes of CPA/EE, overlap with hormonal contraceptive episodes will be assessed similarly to the switches between hormonal contraceptives. However, as concomitant use of CPA/EE and hormonal contraceptives is among the study objectives, we will not define a switch but classify in terms of (potential) concomitant use. The days between the adjusted end date and the original end date of a truncated episode will be classified as:

- Potential concomitant use: (see Figure 9.2) when a "switch" from CPA/EE to a hormonal contraceptive *or vice versa* occurs during the last prescription within a treatment episode
- Concomitant use: when both start and end date of a hormonal contraceptive episode lie between start and end date of a CPA/EE episode *or vice versa*; or when a "switch" from CPA/EE to a hormonal contraceptive *or vice versa* precedes the last prescription within a treatment episode**.**
- Non-concomitant use: both start and end date of a hormonal contraceptive episode lie outside a CPA/EE episode (i.e. before or after both start and end date of a CPA/EE episode).
- No use of hormonal contraceptives (no observed treatment episodes of hormonal contraceptives within 365 days before the index date until end of follow-up).

Because the validity of estimating duration differs between administration routes (oral, intra-uterine, implant, injection, ring and patch) concomitant use will be computed separately and presented separately in text or tables, depending on the numbers observed.

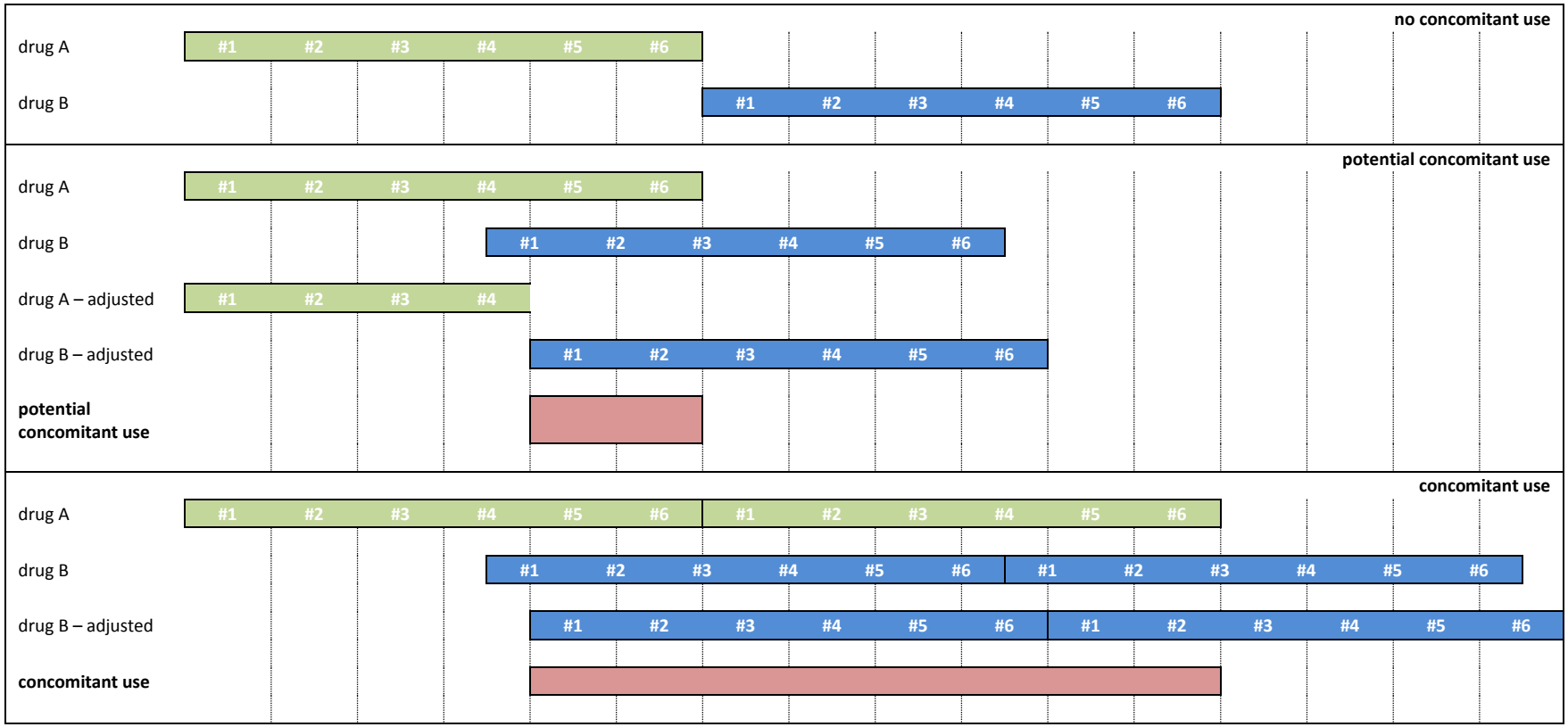

Figure 9.2 Definition of potential concomitant use of CPA/EE and hormonal contraceptives

9.4 Data sources

The study will be conducted in three databases: the PHARMO Database Network (PHARMO) in The Netherlands, The Health Improvement Network (THIN) in the United Kingdom and the Health Search Database (HSD) in Italy. These databases have also been used in the EMA commissioned study "Patterns and Determinants of Use of Oral Contraceptives in the European Union" (EMA/2001/37/CN). A fact sheet from this study can be found on www.pharmo.com under 'Partners – EU Collaborations'.

9.4.1 PHARMO Database Network - The Netherlands

The PHARMO Database Network includes several linked databases which contain data on patient demographics, mortality, drug dispensings, hospital morbidity, laboratory, pathology and general practitioner information from more than 4 million inhabitants in defined areas of the Netherlands. The different databases are linked through probabilistic linkage methods. There is a gatekeeper function by the general practitioner (GP) and the GP Database will be best suited to identify diagnoses such as acne and hirsutism. The Out-patient Pharmacy Database will be used as a data source for identification of dispensings of CPA/EE, hormonal contraceptives and acne medication as the GP is not directly involved in refill dispensings. Patient demographics, treatment characteristics and (concomitant) use of hormonal contraceptives will be studied in this population. Diagnoses of acne, hirsutism and other hyperandrogenic conditions are captured in the GP database and therefore previous diagnosis of acne, hirsutism or other hyperandrogenic conditions and previous acne treatment (by presence or absence of acne diagnosis) will be studied in the overlapping population between the Out-patient Pharmacy Database and the GP database. Current size of the overlapping population is ca. 1.1 million.
The PHARMO Database Network has already been used for several studies in the field of hormonal contraceptives. Throughout this report, note that "prescription" refers to "dispensing" for the PHARMO data.

GP database

The General Practitioner (GP) Database comprises data from electronic patient records registered by GPs. The records include information diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescriptions records include information on type of product, date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO Anatomical Therapeutic Chemical (ATC) Classification System (www.whocc.no/atc_ddd_index). Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) (https://www.nhg.org/themas/artikelen/icpc), which can be mapped to ICD codes, but can also be entered as free text. GP data cover a catchment area representing 3.2 million residents.

Out-patient Pharmacy Database

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, and quantity, route of administration, prescriber specialty and costs. Drug dispensings are coded according to the WHO Anatomical Therapeutic Chemical (ATC)

Classification System (www.whocc.no/atc_ddd_index). Out-patient pharmacy data cover a catchment area representing 4.2 million residents.

9.4.2 The Health Improvement Network (THIN) – United Kingdom

The Health Improvement Network (THIN) database is a longitudinal, primary care database that contains diagnostic and prescribing information recorded by the GPs as part of their routine medical practice. General practitioners are gatekeepers in the UK national health system and in THIN data on ca. 4 million active patients are captured.

In general there is a good coverage of OC prescriptions in THIN (some exceptions exist, e.g. prescriptions from family planning clinics are not recorded), although, in the UK, general practice is cited as the most common provider of contraceptives for women[3]. The database has already been used for drug utilization studies on contraceptive methods[4-7]. In the UK, contraceptives have been provided free of prescription charges since 1974, and continuation rates and switching patterns are unlikely to be influenced by the costs of the individual contraceptives and the required logistics for refilling prescriptions. Ambulatory diagnosis such as acne, hirsutism and polycystic ovary syndrome (PCOS) would generally be recorded and coded by the GP, as well as acne treatments, as long as they are prescription drugs. The use of primary care databases such as THIN is a well-accepted method for examining drug use in broad patient populations.

9.4.3 Health Search Database (HSD) - Italy

The Health Search/Longitudinal Patients Database (HSD) is a primary care database that was established in 1998 by the Italian College of General Practitioners. It contains data from computer-based patient records of more than 800 GPs from all Italian regions, covering a population of ca. 1.3 million active patients. The GPs voluntarily agreed to collect data and after attending training have to use specifically designed software to record data during their normal daily clinical practice. The database includes information on patient demographics, GP registration information, drug prescriptions, diagnoses, tests and test results and date of death. In general, hormonal contraceptive prescriptions are reliably recorded in HSD and the database was part of the EMA commissioned study "Patterns and Determinants of Use of Oral Contraceptives in the European Union" (EMA/2001/37/CN). Diagnosis such as acne, hirsutism and polycystic ovary syndrome (PCOS) would generally be recorded and coded by the GP, as well as acne treatments, as long as they are prescription drugs. With regard to capture of hormonal contraceptive use, it is acknowledged that the data is not exhaustively captured in the database. The underestimation is mainly due to private prescriptions. HSD is the only data source to have part of private prescription (claims database do not have it at all) and, given that the indication of drug use is relevant for this protocol, HS is the only data source to possess it in Italy.

9.5 Study Size

In a preliminary analysis of 2011-2012 about 9,000 new users of CPA/CEE were observed across the databases: 2,700 new users in PHARMO, 5,600 new users in THIN and 700 new users were observed in HSD.

9.6 Data management

9.6.1 PHARMO Database Network - The Netherlands

The PHARMO Database Network combines data from different healthcare databases (pharmacy, hospital, GP etc.). These different databases are probabilistically linked through validated algorithms that do not invade the privacy of the patients. Before linkage of the different databases, patients for whom crucial information needed for linkage is missing (date of birth, gender, GP) are removed.

Healthcare databases are used as administration tools in patient care and have their limitations with regard to their use in scientific research. For example, the completeness of data may differ per healthcare centre. Therefore, with each update of the database the completeness of registration per healthcare centre is evaluated (overall and within specific care areas, number of records, internal consistency and comparison of calendar years).

For each study, specific study checks on the linked data are performed. These partially depend on which specific databases are required for the study and their importance to the selection of patients or outcomes. For each database it is determined per patient from which time point onwards the patient is registered in the specific database and from which time point the patient is lost to follow-up (due to for example death or moving out of the PHARMO catchment area). Patients are regarded eligible to be included in a study if they are registered and can be followed in all required databases.

Study data are manipulated and analysed using the utility SAS Enterprise Guide, an environment for SAS enabling the storage of syntaxes or codes belonging to a single study in one project file, subdivided into project flows for different aspects of a study.

9.6.2 The Health Improvement Network (THIN) – United Kingdom

The Health Improvement Network (THIN) is a collaboration between two companies, In Practice Systems Ltd. (INPS), developer of Vision software used by GPs in the UK, and EPIC, provider of access to data for use in medical research. THIN data are collected during routine practice and regularly delivered to THIN. THIN data collection started in 2003, currently contains the electronic medical records of almost 8 million patients (more than 3 million active patients) collected from over 386 general practices in the UK covering more than 5.7% of the population in the UK[8]. Patient data are arranged in four standardized (Patient, Medical, Therapy and Additional Health Data and one linked (postcode variable indicators) files per practice. Further information is possible to obtain via the Additional Information Service (AIS) including: questionnaires completed anonymously by the patient or GP, copies of patient-based correspondence, a specified intervention (e.g. a laboratory test to confirm diagnosis) and death certificates

9.6.3 Health Search Database (HSD) - Italy

HSD contains information recorded by GPs only. Patients' demographic details are linked through the use of an encrypted code with clinical records (diagnoses, referrals, and tests results), drug prescriptions (drug name, date of filled prescription, and number of days' supply), prevention records, hospital admissions, and date of death. Free-text files are also available.

To be considered for participation in epidemiological studies, GPs should meet "up-to-standard" quality criteria pertaining to the levels of coding, prevalence of well-known diseases, mortality rates, and years of recording. The "data quality" checking is performed every semester.

Study data can be manipulated and analysed using SQL, Stata or SAS syntaxes.

9.7 Data analysis

Patient, treatment and diagnosis characteristics will be reported descriptively. Categorical data will be presented as counts (n) and proportions (%). Continuous data will be presented as means with standard deviation (SD) and as medians with inter quartile range (IQR) when appropriate. Results will be stratified by year of index date. Table shells are presented in Annexes 1 and 2 (sections 14 and 15).

9.8 Quality control

Standard operating procedures at each research centre will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.
All programming written by the executing researcher will be reviewed independently by a senior researcher. All key study documents, such as the statistical analysis plan and study reports, will undergo quality control and senior scientific review.

9.9 Limitations of the research methods

Drug utilization studies conducted in automated healthcare databases allow identification of patients who are prescribed or dispensed the drugs of interest and characterisation of these patients according to prior medical history, use of medications, and patterns of use of medications. Healthcare databases have become a useful tool for conducting research to study the safety of drugs as information on diagnoses and treatments is recorded on an ongoing basis.

Limitations regarding treatment

Healthcare databases are used as administration tools in patient care and have their limitations with regard to their use in scientific research, mainly related to the type and completeness of the recorded information. Regarding treatment data, databases provide detailed information on prescribed and/or dispensed medications but not on the actual use of the medications by patients. Thus, patients may be classified as exposed when they are not actually taking the drug. Furthermore, databases often do not record the intended duration of use of each prescription (days of supply). This needs to be estimated from the interval between consecutive prescriptions and can result in misclassification of drug exposure. In particular the use of long-acting hormonal contraceptives (intra-uterine devices, injections and implants) may be misclassified. To be eligible for inclusion in our study, women were requested to have at least one year enrolled with the general practitioner, this eligibility criterion may result into some misclassification of exposure of these devices in both directions, potential for false negatives (underecorded use (earlier the year prior index date) or false positivies (removal or ended life cycle of these devices at the time of index date or during the year after). However, we expect the use of LARC to be low in this population, as women initiating CPA are expected to be on average 20-23 years old[7]. As the indication of use is not recorded for most of the prescriptions, the identification of the indication depends on concomitantly recorded diagnoses. Another limitation of the assessment of medication use from databases is that over-the-counter medications are usually not recorded. As OTC medications do play an important role in the treatment of acne the limitation of not recording those needs to be taken into consideration when interpreting the results. Furthermore, as discussed in

the context of information on prescriber (section 9.3), in GP databases only GP prescriptions are recorded, not specialist prescriptions, e.g. from gynaecologists. Completeness of recording of refill dispensings in the GP (prescription) database varies by database.

Limitations regarding diagnoses

Databases of electronic medical records are restricted to information recorded to serve the purpose of the database: primary care, claims, etc. Because these databases were not designed to perform research, underreporting of events may occur. As mentioned in the previous section, this underreporting may limit the assignment of indication of use. In addition, it should be noted that the actual indication may have changed, e.g. in the case of CPA/CEE, some users may have started with the indication acne, but continue after some time because of the contraceptive effect.

9.10 Other aspects

None.

10. Protection of human subjects

The study will be conducted in accordance with Good Epidemiology Practices[9]. This is a retrospective, non-interventional study and does not pose any risks for patients. All data used for the study will be de-identified with no breach of confidentiality with regards to personal identifiers or health information. Each database research partner will apply for an independent ethics committee review and/or other approvals according to local regulations.

Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study subjects.

10.1 PHARMO Database Network - The Netherlands

The PHARMO Institute conducts research according to the latest directives regarding privacy and handling of data. The PHARMO Database Network combines data from different sources (pharmacy, hospital, laboratory etc.). Some of these databases are managed by PHARMO in-house and no permissions are required for access to data. For partnership databases, permissions are required for access to data. The various databases are probabilistically linked through validated algorithms that do not invade the privacy of the patients. Researchers only have access to data depleted of sensitive personal information (such as date of birth) that may be traced back to persons and study reports will contain aggregate data only. This approach is approved by the Dutch Data Protection Authority. Because of the use of de-identified data from existing databases without any direct enrolment of subjects, ethical approval or informed consent is not necessary according to the Dutch law regarding human medical scientific research (Wet medisch-wetenschappelijk onderzoek met mensen (WMO)), which is enforced by the Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek, CCMO).

10.2 The Health Improvement Network (THIN) – United Kingdom

Centro Español de Investigación Farmacoepidemiológica (CEIFE) will comply with all applicable data protection, security and privacy laws, rules and regulations with respect to the collection, production, use, processing, storage, transfer, modification, deletion, and/or disclosure of any

information related to this study under this Agreement. CEIFE will ensure that information is not disclosed or transferred to any third party not mentioned in this protocol. CEIFE will ensure that appropriate technical and organizational measures are taken to protect information against accidental or unlawful destruction or accidental loss or alteration, or unauthorized disclosure or access and against all other unlawful forms of processing. CEIFE will store the Database used to perform this study at the premises of CEIFE. Privacy issues will be addressed and respected at each stage of the study. All analyses and reporting will be done on appropriately de-identified data and only in aggregate form. We will abide by the Guidelines for Good Pharmacoepidemiology Practices.[9] The study protocol is dependent on approval by a Scientific Research Committee (SRC) for studies performed in THIN.

10.3 Health Search Database (HSD) - Italy

The Health Search institute (at Genomedics S.R.L.) has data from GPs, who registered clinical information on their patients during their daily clinical activity.
Given the use of encrypted data from an existing database without any direct enrolment of subjects, ethical approval or informed consent is not necessary according to the Italian law regarding human medical scientific research.

11. Management and reporting of adverse events/adverse reactions

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. No expedited reporting of adverse events or reactions is required.

12. Plans for disseminating and communicating study results

Study protocol, study status, and report(s) will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Report, and other regulatory milestones and requirements.

Study results will be published following guidelines of the International Committee of Medical Journal Editors[10], and communication in appropriate scientific venues, e.g., International Society for Pharmacoepidemiology, will be considered.

When reporting results of this study, the appropriate STROBE checklist will be followed[11].

13. List of references

1. Vessey MP, Doll R. Investigation of relation between use of oral contraceptives and thromboembolic disease. A further report. *British medical journal* 1969; **2**(5658): 651-7.
2. Nast A, Dréno B, Bettoli V, et al. European Evidence-based (S3) Guidelines for the Treatment of Acne. *Journal of the European Academy of Dermatology and Venereology* 2012; **26**: 1-29.
3. French RS, Mercer CH, Johnson AM, Fenton KA, Erens B, Wellings K. Use of contraceptive services in Britain: findings from the second National Survey of Sexual Attitudes and Lifestyles (Natsal-2). *The journal of family planning and reproductive health care / Faculty of Family Planning & Reproductive Health Care, Royal College of Obstetricians & Gynaecologists* 2009; **35**(1): 9-14.
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5. Cea Soriano L, Wallander MA, Andersson SW, Requena G, Garcia-Rodriguez LA. Study of long-acting reversible contraceptive use in a UK primary care database: validation of methodology. *The European journal of contraception & reproductive health care : the official journal of the European Society of Contraception* 2014; **19**(1): 22-8.
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10. ICMJE. Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals. 2013. http://www.icmje.org/icmje-recommendations.pdf (accessed 13 August 2014).
11. Strobe. Strobe statement - strengthening the reporting of observational studies in epidemiology. 2007. http://www.strobe-statement.org/pdf/index.php?id=available-checklists (accessed 13 August 2014).

14. Annex 1. Additional information: figure and table shells

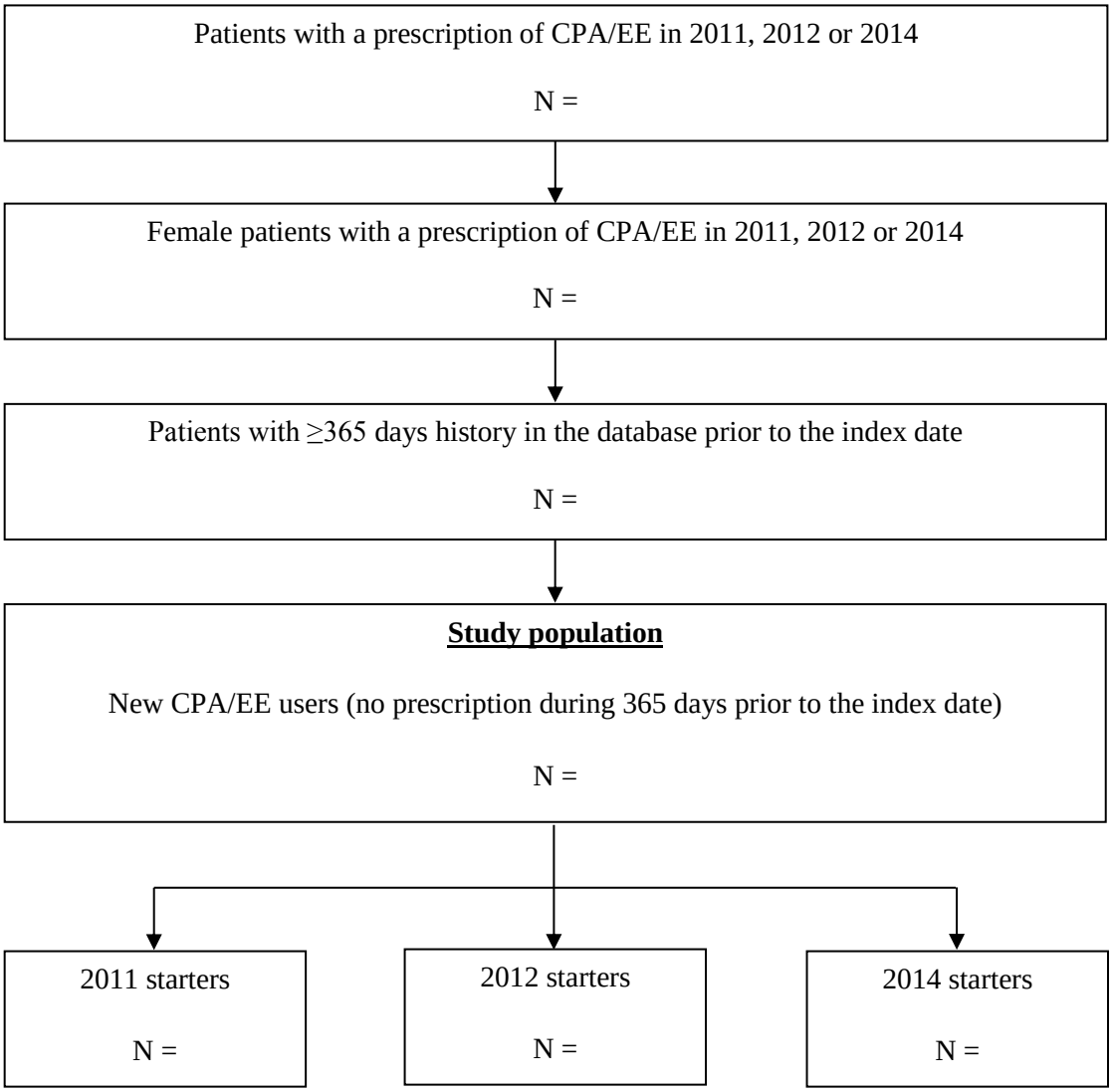


Figure 14.1 Flow chart of patient selection in PHARMO

NOTE: in the interim report only data from the first run (2011/2012 users) will be available.

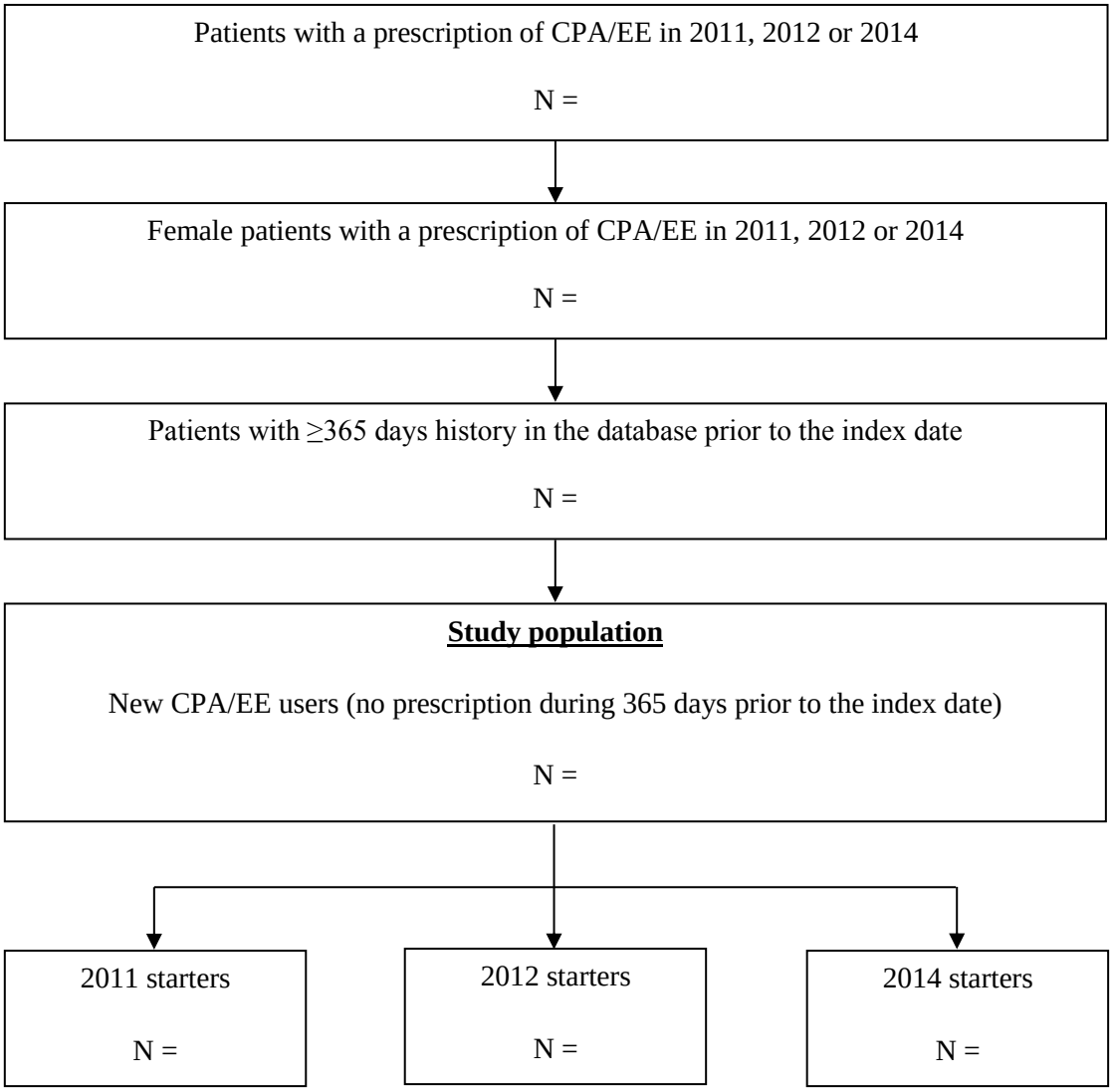


Figure 14.2 Flow chart of patient selection in THIN

NOTE: in the interim report only data from the first run (2011/2012 users) will be available.

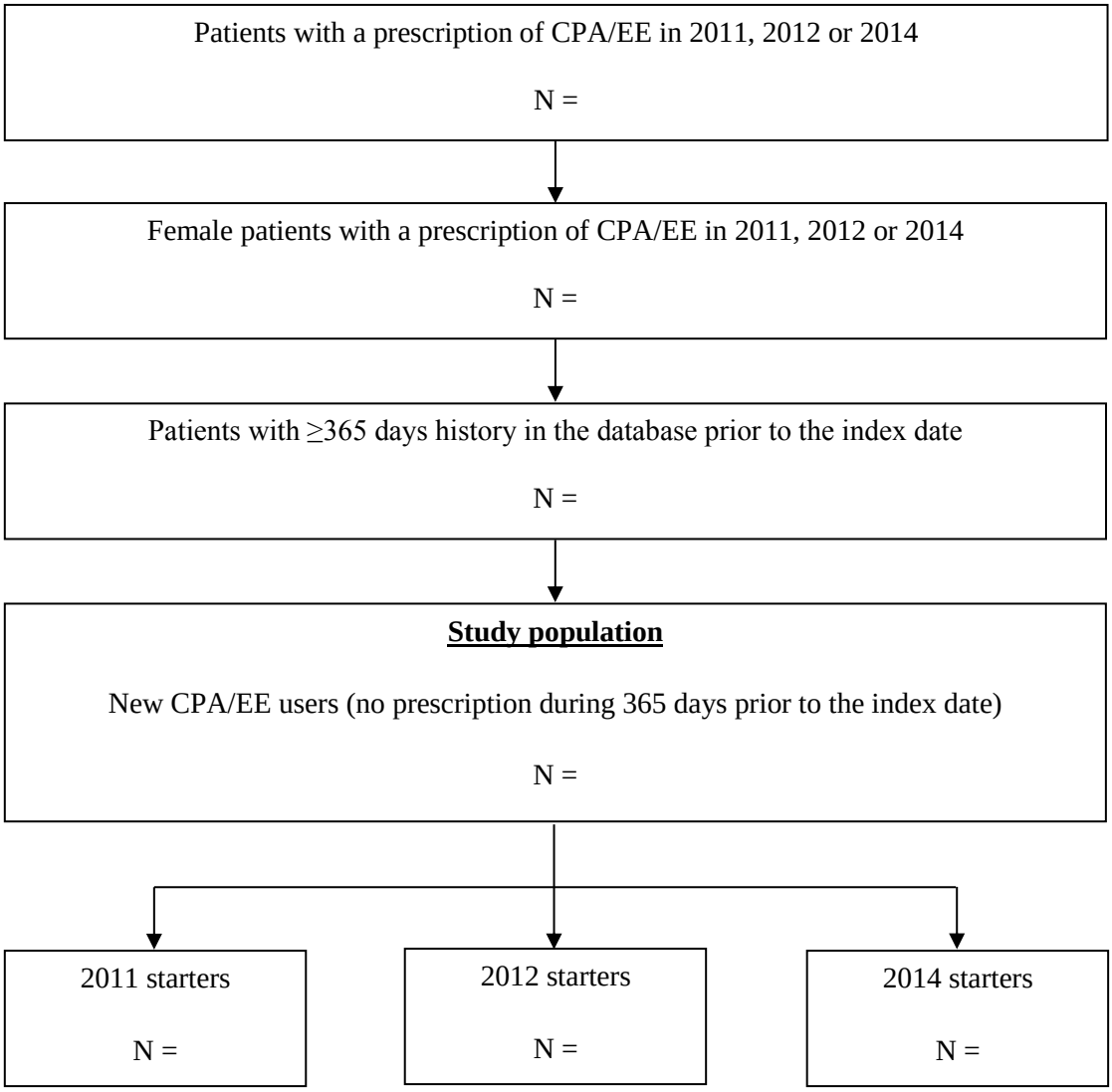


Figure 14.3 Flow chart of patient selection in HSD

NOTE: in the interim report only data from the first run (2011/2012 users) will be available.

Table 14.1 General characteristics of new CPA/EE users in PHARMO, THIN and HSD in 2011-2012

	PHARMO	**THIN**	**HSD**
	2011/2012 starters N = n (%)	**2011/2012 starters N = n (%)**	**2011/2012 starters N = n (%)**
Age (years)			
<15			
15-<25			
25-<35			
35-<45			
45-<55			
≥55			
mean ± SD			
median (IQR)			
Database history before index date (years)			
1-<2			
2-4			
>4			
mean ± SD			
median (IQR)			
Follow-up after index date (months)*			
<6			
6-12			
13-24		n.a.	n.a.
mean ± SD			
median (IQR)			

*by definition, the follow-up will not be longer than 24 months (start study period January 1, 2011, end study period December 31, 2012).

Table 14.2 General characteristics of new CPA/EE users in PHARMO, THIN and HSD in 2011, 2012 and 2014

	PHARMO			**THIN**			**HSD**		
	2011 starters N = n (%)	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**
Age (years)									
<15									
15-<25									
25-<35									
35-<45									
45-<55									
≥55									
mean ± SD									
median (IQR)									
Database history before index date (years)									
1-<2									
2-4									
>4									
mean ± SD									
median (IQR)									
Follow-up after index date (months)*									
<6									
6-12									
13-24	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
mean ± SD									
median (IQR)									

*by definition, the follow-up will not be longer than 12 months (end of study period is defined as December 31st of the year of the index date).

NOTE: in the interim report only data from the first run (2011/2012 users) will be available.

Table 14.3 Treatment characteristics of new CPA/EE users in PHARMO, THIN and HSD in 2011-2012

	PHARMO	**THIN**	**HSD**
	2011/2012 starters N = n (%)	**2011/2012 starters N = n (%)**	**2011/2012 starters N = n (%)**
Type of CPA/EE			
Diane 35			
Generic			
Unknown			
CPA/EE prescriber			
GP		n (100%)	n (100%)
Dermatologist		n.a.	n.a.
Gynaecologist		n.a.	n.a.
Other specialist		n.a.	n.a.
Unknown		n.a.	n.a.
Number of CPA/EE episodes during follow-up			
1-2			
3-4			
≥5			
mean ± SD			
median (IQR)			
Summed duration of CPA/EE use (months)*			
<6			
6-12			
13-24		n.a.	n.a.
mean ± SD			
median (IQR)			
Concomitant use of CPA/EE and HC**†			
Concomitant			
Potential concomitant			
Non-concomitant			
No use of HC			
Duration of concomitant use of CPA/EE and HC**†			
≤28 days concomitant use			
>28 - 84 days concomitant use			
>84 days concomitant use			
mean ± SD			
median (IQR)			
Duration of potential concomitant use of CPA/EE and HC**†			
≤28 days potential concomitant use			
>28 - 84 days potential concomitant use			
>84 days potential concomitant use			
mean ± SD			

median (IQR)		

*follow-up is maximum 24 months; †users of CPA/EE may occur in multiple categories of concomitant use if more than one episode of HC is observed.

Table 14.4 Treatment characteristics of new CPA/EE users in PHARMO, THIN and HSD in 2011, 2012 and 2014

	PHARMO			**THIN**			**HSD**		
	2011 starters N = n (%)	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**
Type of CPA/EE									
Diane 35									
Generic									
Unknown									
CPA/EE prescriber									
GP				n (100%)	n (100%)	n (100%)	n (100%)	n (100%)	n (100%)
Dermatologist				n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Gynaecologist				n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other specialist				n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Unknown				n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Number of CPA/EE episodes during follow-up									
1-2									
3-4									
≥5									
mean ± SD									
median (IQR)									
Summed duration of CPA/EE use (months)*									
<6									
6-12									
13-24	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
mean ± SD									
median (IQR)									
Concomitant use of CPA/EE and HC**†									
Concomitant									
Potential concomitant									
Non-concomitant									
No use of HC									
mean ± SD									
median (IQR)									
Duration of concomitant use of CPA/EE and HC**†									
≤28 days concomitant use									
>28 - 84 days concomitant use									
>84 days concomitant use									
Duration of potential concomitant use of CPA/EE and HC**†									
≤28 days(potential									

concomitant use >28 - 84 days potential concomitant use >84 days potential concomitant use mean ± SD median (IQR)			

*follow-up is maximum 12 months; †users of CPA/EE may occur in multiple categories of concomitant use if more than one episode of HC is observed.

NOTE: in the interim report only data from the first run (2011/2012 users) will be available.

Table 14.5 Treatment of acne among new CPA/EE users in the year prior to index date in PHARMO, THIN and HSD in 2011-2012

	PHARMO	**THIN**	**HSD**
	2011/2012 starters N = n (%)	**2011/2012 starters N = n (%)**	**2011/2012 starters N = n (%)**
Users **with** acne diagnosis	N = n (%)	N = n (%)	N = n (%)
Topicals Topical antibiotics Corticosteroids in topical combinations Topical retinoids Other topical preparations Systemic preparations Systemic retinoids Systemic antibiotics Hormonal agents Hormonal contraceptives Antiandrogens			
Users **without** acne diagnosis	N = n (%)	N = n (%)	N = n (%)
Topicals Topical antibiotics Corticosteroids in topical combinations Topical retinoids Other topical preparations Systemic preparations Systemic retinoids Systemic antibiotics Hormonal agents Hormonal contraceptives Antiandrogens			

Table 14.6 Treatment of acne among new CPA/EE users in the year prior to index date in PHARMO, THIN and HSD in 2011, 2012 and 2014

	PHARMO			**THIN**			**HSD**		
	2011 starters N = n (%)	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**
Users **with** acne diagnosis	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)
Topicals Topical antibiotics Corticosteroids in topical combinations Topical retinoids Other topical preparations Systemic preparations Systemic retinoids Systemic antibiotics Hormonal agents Hormonal contraceptives Antiandrogens									
Users **without** acne diagnosis	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)	N = n (%)
Topicals Topical antibiotics Corticosteroids in topical combinations Topical retinoids Other topical preparations Systemic preparations Systemic retinoids Systemic antibiotics Hormonal agents Hormonal contraceptives Antiandrogens									

NOTE: in the interim report only data from the first run (2011/2012 users) will be available.

Table 14.7 Diagnoses of hyperandrogenic conditions among new CPA/EE users in the year prior to index date in PHARMO, THIN and HSD in 2011-2012

	PHARMO	**THIN**	**HSD**
	2011/2012 starters N = n (%)	**2011/2012 starters N = n (%)**	**2011/2012 starters N = n (%)**
Acne			
Alopecia			
Contraceptive management			
Hirsutism			
Menstrual problems			
Oligomenorrhoea/amenorrhoea			
Polycystic ovary syndrome			
Seborrhea			

Table 14.8 Diagnoses of hyperandrogenic conditions among new CPA/EE users in the year prior to index date in PHARMO, THIN and HSD in 2011, 2012 and 2014

	PHARMO			**THIN**			**HSD**		
	2011 starters N = n (%)	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**	**2011 starters N = n (%)**	**2012 starters N = n (%)**	**2014 starters N = n (%)**
Acne									
Alopecia									
Contraceptive management									
Hirsutism									
Menstrual problems									
Oligomenorrhoea/amenorrhoea									
Polycystic ovary syndrome									
Seborrhoea									

NOTE: in the interim report only data from the first run (2011/2012 users) will be available.

15. Annex 2. Additional information: figure and table shells for 2017 objectives

15.1 Patient selection and characteristics

15.1.1 Patient selection and characteristics in PHARMO

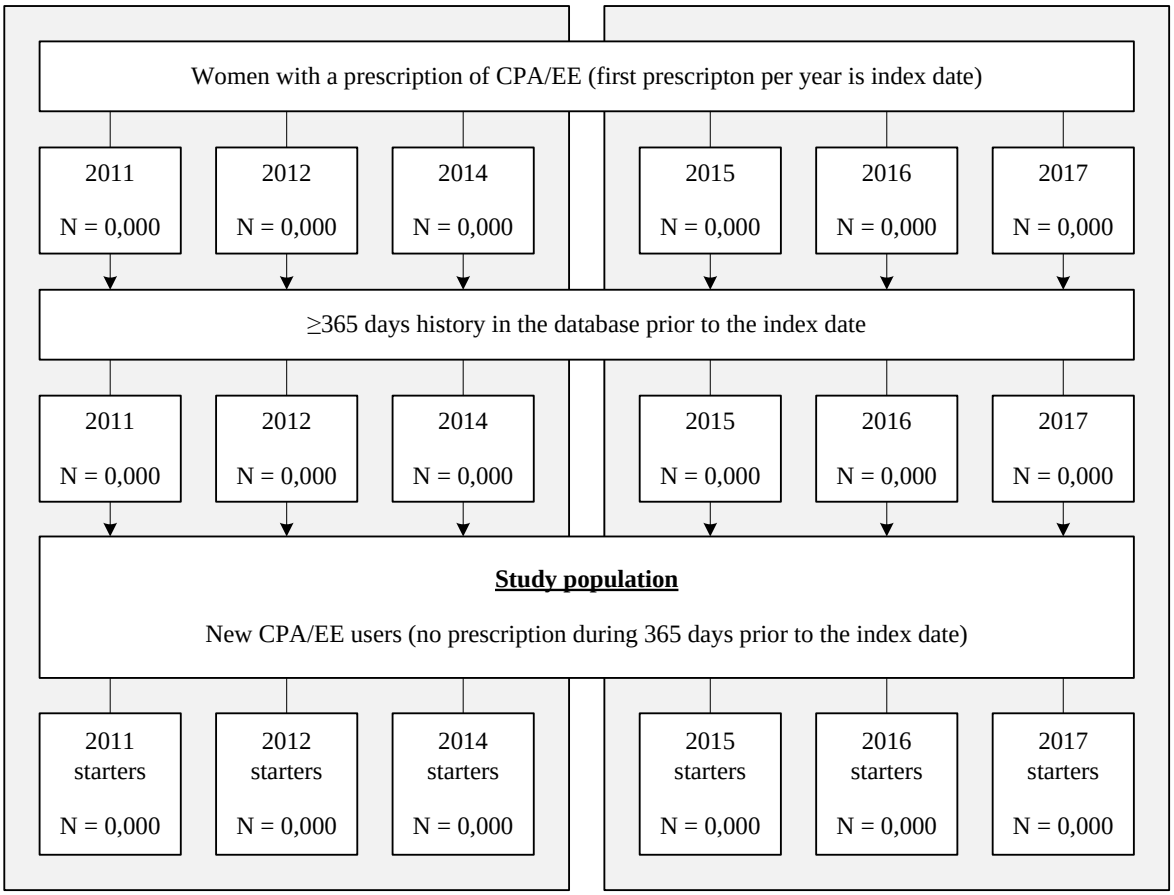


Figure 15.1 Flow chart of patient selection in PHARMO

NOTE: this flow chart will be repeated for each database. An additional level of 'GP data available' will be added for PHARMO

Table 15.1 General characteristics of new CPA/EE users in PHARMO per calendar year

	2011 starters N=7,876 n (%)	**2012 starters N=7,562 n (%)**	**2014 starters N=1,401 n (%)**	**2015 starters N=0,000 n (%)**	**2016 starters N=0,000 n (%)**	**2017 starters N=0,000 n (%)**
Age (years)						
<15	278 (4)	262 (3)	13 (1)			
15-<25	3,986 (51)	3,733 (49)	482 (34)			
25-<35	2,385 (30)	2,365 (31)	584 (42)			
35-<45	1,001 (13)	968 (13)	242 (17)			
45-<55	211 (3)	229 (3)	73 (5)			
≥55	15 (<0.5)	5 (<0.5)	7 (<0.5)			
mean ± SD	25 ± 9	25 ± 9	29 ± 9			
median (IQR)	23 (18-31)	24 (18-31)	27 (23-34)			
Database history before index date (years)						
1-<2	420 (5)	418 (6)	91 (6)			
2-4	966 (12)	648 (9)	140 (10)			
>4	6,490(82)	6,496 (86)	1,170 (84)			
mean ± SD	8 ± 4	9 ± 4	9 ± 5			
median (IQR)	7 (5-12)	8 (6-13)	9 (6-11)			
Follow-up after index date (months)*						
<6	3,877 (49)	3,573 (47)	641 (46)			
6-12	3,999 (51)	3,989 (53)	760 (54)			
mean ± SD	6 ± 3	6 ± 3	6 ± 3			
median (IQR)	6 (3-9)	6 (3-9)	6 (3-9)			

* by definition, the follow-up will not be longer than 12 months (see section 9.2).

15.1.2 Patient selection and characteristics in THIN

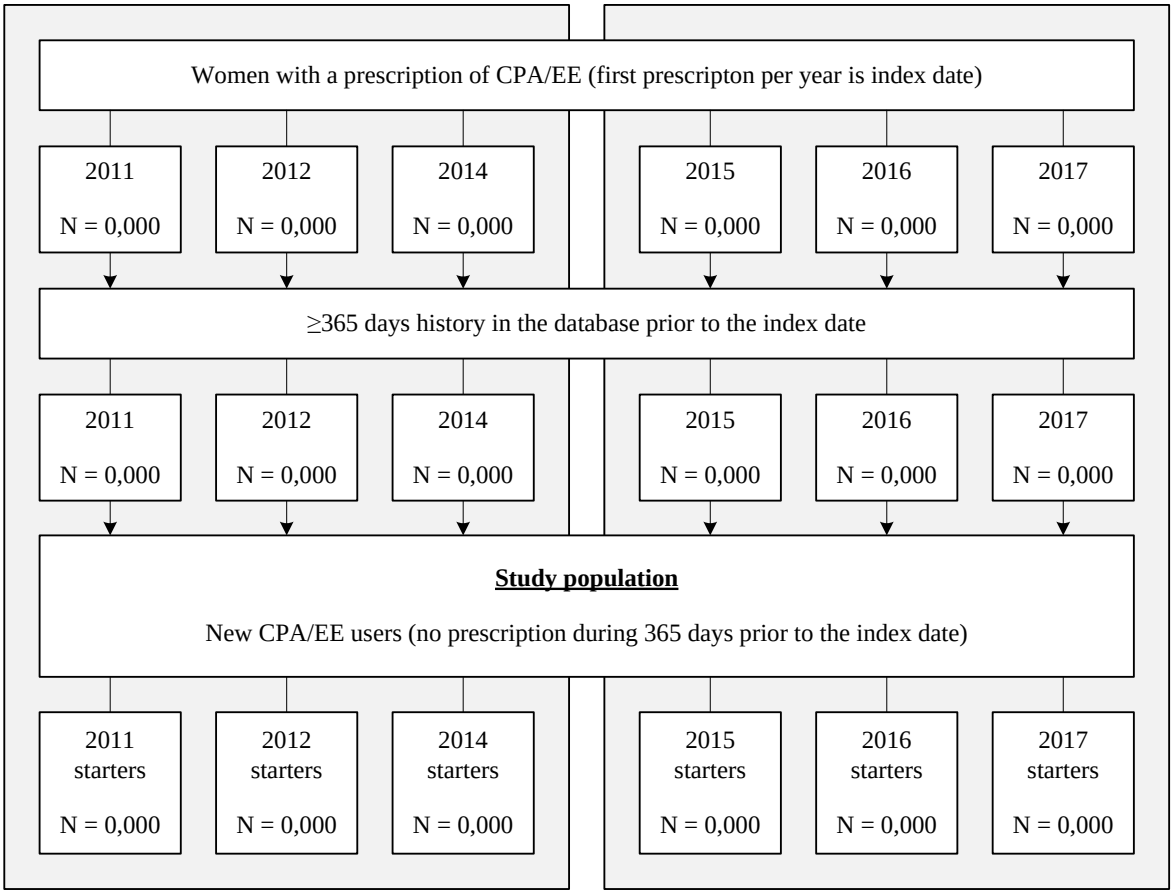


Figure 15.2 Flow chart of patient selection in THIN

Table 15.2 General characteristics of new CPA/EE users in THIN per calendar year

	2011 starters N=2,760 n (%)	**2012 starters N=2,923 n (%)**	**2014 starters N=2,341 n (%)**	**2015 starters N=0,000 n (%)**	**2016 starters N=0,000 n (%)**	**2017 starters N=0,000 n (%)**
Age (years)						
<15	154 (6)	175 (6)	136 (6)			
15-<25	1,520 (55)	1,617 (55)	1,310 (56)			
25-<35	866 (31)	907 (31)	709 (30)			
35-<45	208 (8)	209 (7)	176 (8)			
45-<55	11 (<0.5)	14 (<0.5)	10 (<0.5)			
≥55	1 (<0.5)	1 (<0.5)	0 (0)			
mean ± SD	23 ± 7	23 ± 7	23 ± 7			
median (IQR)	22 (17-28)	22 (17-28)	22 (17-28)			
Database history before index date (years)						
1-<2	171 (6)	219 (7)	163 (7)			
2-4	248 (9)	223 (8)	179 (8)			
>4	2,341 (84)	2,481 (85)	1,999 (85)			
mean ± SD	11 ± 6	12 ± 6	12 ± 7			
median (IQR)	12 (6-16)	12 (6-16)	13 (7-17)			
Follow-up after index date (months)*						
<6	1,316 (48)	1,351 (46)	1,108 (47)			
6-12	1,444 (52)	1,572 (54)	1,233 (53)			
mean ± SD	6 ± 4	6 ± 4	6 ± 4			
median (IQR)	6 (3-9)	6 (3-9)	6 (3-9)			

* by definition, the follow-up will not be longer than 12 months (see section 9.2).

15.1.3 Patient selection and characteristics in HSD

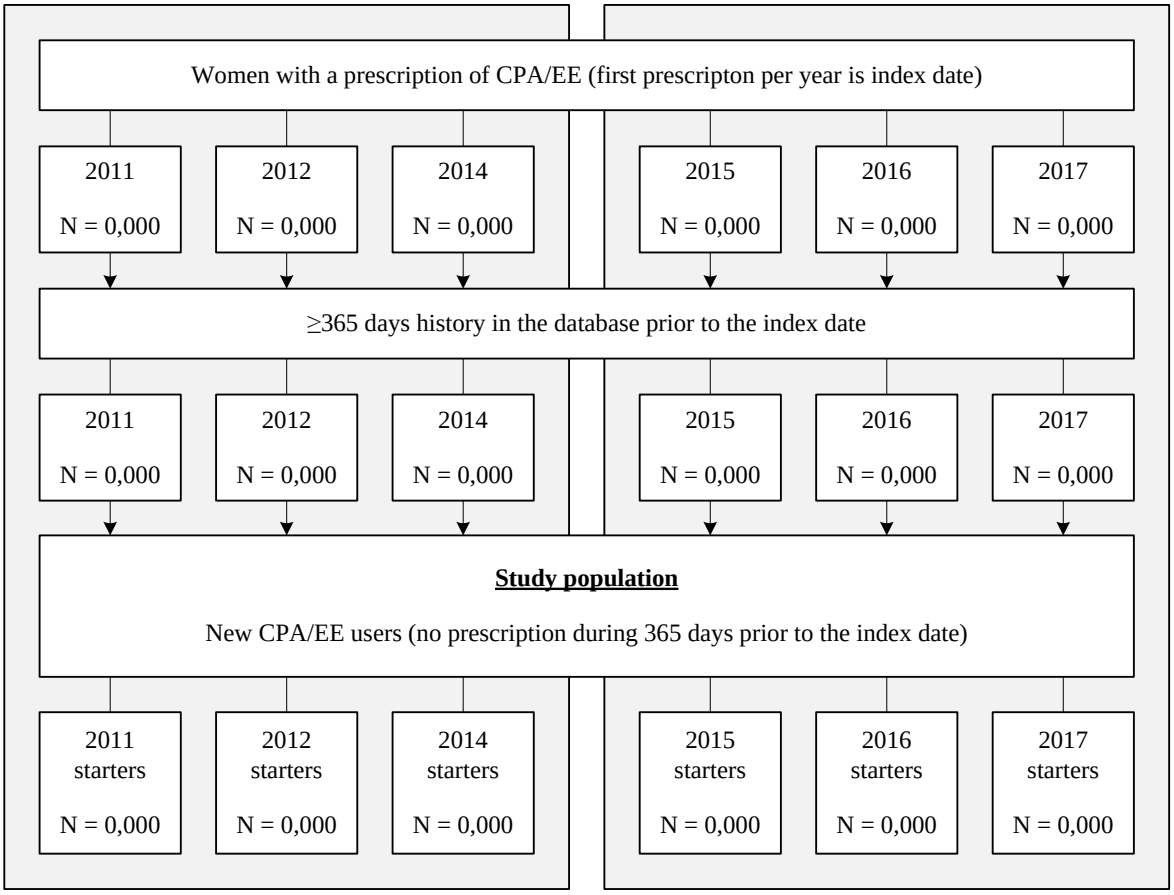


Figure 15.3 Flow chart of patient selection in HSD

Table 15.3 General characteristics of new CPA/EE users in HSD per calendar year

	2011 starters N=495 n (%)	**2012 starters N=446 n (%)**	**2014 starters N=261 n (%)**	**2015 starters N=0,000 n (%)**	**2016 starters N=0,000 n (%)**	**2017 starters N=0,000 n (%)**
Age (years)						
<15	5 (1)	0 (0)	1 (<0.5)			
15-<25	207 (42)	212 (48)	105 (40)			
25-<35	146 (29)	120 (27)	83 (32)			
35-<45	93 (19)	71 (16)	47 (18)			
45-<55	36 (7)	33 (7)	19 (7)			
≥55	8 (2)	10 (2)	6 (2)			
mean ± SD	29 ± 10	29 ± 10	29 ± 11			
median (IQR)	26 (21-36)	25 (21-35)	26 (21-36)			
Database history before index date (years)						
1-<2	18 (4)	14 (3)	11 (4)			
2-4	41 (8)	36 (8)	27 (10)			
>4	436 (88)	396 (89)	223 (85)			
mean ± SD	11 ± 7	11 ± 6	12 ± 7			
median (IQR)	11 (6-15)	11 (7-15)	12 (7-16)			
Follow-up after index date (months)*						
<6	232 (47)	224 (50)	118 (45)			
6-12	263 (53)	222 (50)	143 (55)			
mean ± SD	6 ± 4	6 ± 4	6 ± 4			
median (IQR)	6 (3-9)	6 (3-9)	7 (3-10)			

* by definition, the follow-up will not be longer than 12 months (see section 9.2).

15.2 Concomitant use of hormonal contraceptives

15.2.1 Concomitant use of hormonal contraceptives in PHARMO

Table 15.4 Concomitant use of other HC among new CPA/EE users in PHARMO per calendar year

	2011 starters N=0,000 n (%)	**2012 starters N=0,000 n (%)**	**2014 starters N=0,000 (%)**	**2015 starters N=0,000 n (%)**	**2016 starters N=0,000 n (%)**	**2017 starters N=0,000 n (%)**
Number of CPA/EE episodes during follow-up						
1						
2						
≥3						
mean ± SD						
median (IQR)						
Summed duration of CPA/EE use (months) [1)]						
0-3						
4-6						
7-12						
mean ± SD						
median (IQR)						
Concomitant use						
Concomitant and potential concomitant use [2)]						
Potential concomitant use						
Non-concomitant use						
No use of other HC						
Duration of concomitant use of other HC						
≤28 days						
>28 - 84 days						
>84 days						
mean ± SD						
median (IQR)						
Duration of potential concomitant use of other HC (days)						
≤28 days						
>28 - 84 days						
>84 days						
mean ± SD						
median (IQR)						

1) by definition, the follow-up and thus summed duration of use will not be longer than 12 months (see section 9.2).

2) A user may be concomitant and potential concomitant user at different times during CPA/EE use.

15.2.1 Concomitant use of hormonal contraceptives in THIN

Table 15.5 Concomitant use of other HC among new CPA/EE users in PHARMO per calendar year

	2011 starters N=0,000 n (%)	**2012 starters N=0,000 n (%)**	**2014 starters N=0,000 (%)**	**2015 starters N=0,000 n (%)**	**2016 starters N=0,000 n (%)**	**2017 starters N=0,000 n (%)**
Number of CPA/EE episodes during follow-up						
1						
2						
≥3						
mean ± SD						
median (IQR)						
Summed duration of CPA/EE use (months) [1)]						
0-3						
4-6						
7-12						
mean ± SD						
median (IQR)						
Concomitant use						
Concomitant and potential concomitant use [2)]						
Potential concomitant use						
Non-concomitant use						
No use of other HC						
Duration of concomitant use of other HC						
≤28 days						
>28 - 84 days						
>84 days						
mean ± SD						
median (IQR)						
Duration of potential concomitant use of other HC (days)						
≤28 days						
>28 - 84 days						
>84 days						
mean ± SD						
median (IQR)						

1) by definition, the follow-up and thus summed duration of use will not be longer than 12 months (see section 9.2).

2) A user may be concomitant and potential concomitant user at different times during CPA/EE use.

15.2.2 Concomitant use of hormonal contraceptives in HSD

Table 15.6 Concomitant use of other HC among new CPA/EE users in PHARMO per calendar year

	2011 starters N=0,000 n (%)	**2012 starters N=0,000 n (%)**	**2014 starters N=0,000 (%)**	**2015 starters N=0,000 n (%)**	**2016 starters N=0,000 n (%)**	**2017 starters N=0,000 n (%)**
Number of CPA/EE episodes during follow-up						
1						
2						
≥3						
mean ± SD						
median (IQR)						
Summed duration of CPA/EE use (months) [1)]						
0-3						
4-6						
7-12						
mean ± SD						
median (IQR)						
Concomitant use						
Concomitant and potential concomitant use [2)]						
Potential concomitant use						
Non-concomitant use						
No use of other HC						
Duration of concomitant use of other HC						
≤28 days						
>28 - 84 days						
>84 days						
mean ± SD						
median (IQR)						
Duration of potential concomitant use of other HC (days)						
≤28 days						
>28 - 84 days						
>84 days						
mean ± SD						
median (IQR)						

1) by definition, the follow-up and thus summed duration of use will not be longer than 12 months (see section 9.2).

2) A user may be concomitant and potential concomitant user at different times during CPA/EE use.

16. Annex 3. Additional information: code lists

Table 16.1 ATC codes to identify hormonal contraceptives in PHARMO and HSD

Substance	**ATC code**
Contraceptives for topical use	
plastic IUD with progestogen	G02BA03
vaginal ring with progestogen and estrogen	G02BB01
Hormonal contraceptives for systemic use	
Progestogens and oestrogens, fixed combinations	
Etynodiol and ethinylestradiol	G03AA01
Quingestanol and ethinylestradiol	G03AA02
Lynestrenol and ethinylestradiol	G03AA03
Megestrol and ethinylestradiol	G03AA04
Norethisterone and ethinylestradiol	G03AA05
Norgestrel and ethinylestradiol	G03AA06
Levonorgestrel and ethinylestradiol	G03AA07
Medroxyprogesterone and ethinylestradiol	G03AA08
Desogestrel and ethinylestradiol	G03AA09
Gestodene and ethinylestradiol	G03AA10
Norgestimate and ethinylestradiol	G03AA11
Drospirenone and ethinylestradiol	G03AA12
Norelgestromin and ethinylestradiol	G03AA13
Nomegestrol and estradiol	G03AA14
Chlormadinone and ethinylestradiol	G03AA15
Dienogest and ethinylestradiol	G03AA16
Progestogens and oestrogens, sequential preparations	
Megestrol and oestrogen	G03AB01
Lynestrenol and oestrogen	G03AB02
Levonorgestrel and oestrogen	G03AB03
Norethisterone and oestrogen	G03AB04
Desogestrel and oestrogen	G03AB05
Gestodene and oestrogen	G03AB06
Chlormadinone and oestrogen	G03AB07
Dienogest and oestrogen	G03AB08
Progestogens	
Norethisterone	G03AC01
Lynestrenol	G03AC02
Levonorgestrel	G03AC03
Quingestanol	G03AC04
Megestrol	G03AC05
Medroxyprogesterone	G03AC06

Norgestrienone	G03AC07
Etonogestrel	G03AC08
Desogestrel	G03AC09

NOTE: emergency contraceptives (ATC G03AD) are not included.

Table 16.2 Gemscript codes to identify hormonal contraceptives in THIN

Gemscript	Descriptor
first & later first generation	
90566998	Ethinylestradiol with norethisterone - biphasic 7 x 35mcg+500mcg; 14 x 35mcg+1mg Tablet
90703997	Ethinylestradiol with norethisterone - triphasic 7 x 35+500mcg; 7 x 35+750mcg; 7 x 35mcg+1mg Tablet
90703998	Ethinylestradiol with norethisterone - triphasic 7x35+500mcg; 9x35mcg+1mg; 5x35+500mcg Tablet
92682998	Mestranol with norethisterone Tablet
93280992	ETHINYLOESTRADIOL 50MCG/ETHYNODIOL 1MG MCG TAB
93334992	ETHINYLOESTRADIOL 30MCG/ETHYNODIOL 2MG MCG TAB
94158996	Ethinylestradiol 30microgram / Norethisterone acetate 1.5mg tablets
94158997	Ethinylestradiol 20microgram / Norethisterone acetate 1mg tablets
94408992	ANOVLAR 21 TAB
94994992	ETHINYLOESTRAD. 50MCG/NORETHISTERONE 3MG MCG TAB
94995992	ETHINYLOESTRADIOL/NORETHISTERONE 35 MCG TAB
95289992	MINOVLAR TAB
95338992	NORLESTRIN TAB
95885998	Mestranol 50microgram / Norethisterone 1mg tablets
97470998	Ethinylestradiol with norethisterone and placebo 50mcg + 1mg Tablet
97472998	Ethinylestradiol with norethisterone acetate 50mcg + 1mg Tablet
97474998	Ethinylestradiol with norethisterone acetate 50micrograms + 3mg Tablet
97476998	Ethinylestradiol with norethisterone acetate 50micrograms + 3mg Tablet
97563998	Generic Synphase tablets
98085997	Ethinylestradiol 35microgram / Norethisterone 1mg tablets
98085998	Ethinylestradiol 35microgram / Norethisterone 500microgram tablets
98181997	Ethinylestradiol with norethisterone - triphasic and placebo 7 x 35+500mcg; 7 x 35+750mcg; 7 x 35mcg+1mg Tablet
98181998	Generic Trinovum tablets
98183998	ETHINYL+NORETH 35/500mcg tabs
98185998	MESTRANOL+NORETHIST 50mcg/1mg
98187998	ETHINYL+NORETH 35mcg/1mg tabs
98189998	Generic Binovum tablets
98191998	MESTRANOL+NORETHIST 50mcg/1mg
98193998	ETHINYL+NORETH 35/500mcg tabs
98195998	ETHINYL+NORETH 35mcg/1mg tabs
98207998	ETHINY+NORETH 30mcg/1.5mg tabs
98209998	ETHINYL+NORETH 20mcg/1mg tabs
Second generation	
89080998	Generic Microgynon 30 ED tablets
89213998	Ethinylestradiol with levonorgestrel and placebo 30micrograms + 150micrograms Tablet
89341998	Ethinylestradiol with levonorgestrel 30micrograms + 50micrograms Tablet
90641998	Ethinylestradiol with levonorgestrel - triphasic with placebo 6x30+50mcg; 5x40+75mcg;

	10x30+125mcg Tablet
90644998	Ethinylestradiol with levonorgestrel - triphasic 6x30+50mcg; 5x40+75mcg; 10x30+125mcg Tablet
90647998	Levonorgestrel 250microgram / Ethinylestradiol 50microgram tablets
90650998	Levonorgestrel 250microgram / Ethinylestradiol 30microgram tablets
90654998	Ethinylestradiol 30microgram / Levonorgestrel 150microgram tablets
90972998	Ethinylestradiol 35microgram / Norgestimate 250microgram tablets
94997992	ETHINYLOESTRADIOL/LEVONORGESTREL 30 MCG TAB
95002992	ETHINYLOEST+LEVONOR 50/250mcg
97462998	Generic Logynon ED tablets
97464998	ETHINYL+LEVONOR 30/150mcg tabs
97466998	ETHINYL+LEVONOR 30/250mcg tab
98197998	Generic Logynon tablets
98199998	ETHINYL+LEVONOR 30/150mcg tabs
98201998	ETHINYL+LEVONOR 30/250mcg tab
98203998	ETHINYLOEST+LEVONOR 50/250mcg
98205998	Generic Logynon tablets
99036998	ETHINYL+NORGES 35/250mcg tabs
99047998	Norgestimate with ethinylestradiol 250micrograms + 35micrograms Tablet
3rd generation	
84491998	ETHINYL+GESTODEN 20/75mcg tabs
84492998	ETHINYL+GESTODEN 30/75mcg tabs
90747998	Ethinylestradiol 30microgram / Desogestrel 150microgram tablets
90750998	Ethinylestradiol 20microgram / Desogestrel 150microgram tablets
90757998	Ethinylestradiol with gestodene - triphasic 6 x 30+50mcg; 5 x 40+70mcg; 10 x 30+100mcg Tablet
90760998	Ethinylestradiol with gestodene and placebo 30micrograms + 75micrograms Tablet
90969997	Ethinylestradiol 20microgram / Gestodene 75microgram tablets
90969998	Ethinylestradiol 30microgram / Gestodene 75microgram tablets
92485998	ETHINYL+GESTODEN 20/75mcg tabs
93263998	ETHINY+GEST+PLAC 30/75mcg tabs
94398997	Gestodene with ethinylestradiol 75microgramwith20microgram Tablet
94398998	Gestodene with ethinylestradiol 75microgramwith30microgram Tablet
94745998	ETHINYL+DESOGES 20/150mcg tabs
94773998	ETHINYL+GESTODEN 30/75mcg tabs
96439997	Desogestrel with ethinylestradiol 150micrograms with 30micrograms tablets
96439998	Desogestrel with ethinylestradiol 150micrograms with 20micrograms tablets
96922998	ETHINYL+GESTODEN 30/75mcg tabs
97670998	Generic Tri-Minulet tablets
97702998	Generic Tri-Minulet tablets
98178998	ETHINYL+DESOGES 30/150mcg tabs
Drospirenone	
53008979	ETHINYLST+DROSPR 20mcg/3mg tab
81032998	Drospirenone with ethinylestradiol 3mg with 20micrograms tablets
86831998	DROSPIR 2mg/ESTRADIOL 1mg tabs
86832998	Estradiol 1mg / Drospirenone 2mg tablets
92571998	ETHINYLESTR+DROSPIR 30mcg/3mg
98852998	Ethinylestradiol 30microgram / Drospirenone 3mg tablets
Dienogest	
82867998	Generic Qlaira tablets

82869998	estradiol valerate and (estradiol valerate with dienogest) tablets
New compounds	
83740978	NOMEGESTROL AND ETHINLYLESTRADIOL
83741978	Estradiol 1.5mg / Nomegestrol 2.5mg tablets
94996992	ETHINYLOESTRAD.50MCG/LYNOESTRENOL 2.5MG MCG TAB
98176998	Ethinylestradiol with lynoestrenol Tablet
Oral Progestogens	
53167979	Desogestrel 75microgram tablets
53168979	DESOGESTREL 75mcg tablets
53169979	DESOGESTREL 75mcg tablets
53171979	Desogestrel 75microgram tablets
61400979	DESOGESTREL 75mcg tablets
82528978	DESOGESTREL 75mcg tablets
83545978	DESOGESTREL 75mcg tablets
85168978	DESOGESTREL 75mcg tablets
90580998	DESOGESTREL 75mcg tablets
90581998	Desogestrel 75microgram tablets
92598998	NORETHISTERONE 1mg tablets
93893998	Norethisterone 350microgram tablets
93986998	Levonorgestrel 30microgram tablets
95699998	Norgestrel 75microgram tablets
96765998	Etynodiol 500microgram tablets
97451998	LEVONORGESTREL 37.5mcg tabs
97452998	LEVONORGESTREL 30mcg tablets
97599998	ETYNODIOL DIACET 500mcg tabs
98170998	LEVONORGESTREL 30mcg tablets
98172998	Norethisterone 350mcg tablet
98174998	Norethisterone 350mcg tablet
Ring	
83186998	Ethinylestradiol 2.7mg / Etonogestrel 11.7mg vaginal delivery system
84617998	Ethinylestradiol 2.7mg / Etonogestrel 11.7mg vaginal delivery system
Patches	
89295998	Norelgestromin with ethinylestradiol 203micrograms + 33.9micrograms/24hours Transdermal patch
91878998	Ethinylestradiol 33.9micrograms/24hours / Norelgestromin 203micrograms/24hours transdermal patches
94918998	ETHINYL+NOREL 600mcg/6mg patch
Injections Progestogens	
Gemscript codes	
85241998	MEDROXYPROGEST 150mg/1mL inj
85242998	Medroxyprogesterone 150mg/1ml suspension for injection pre-filled syringes
94485998	Medroxyprogesterone acetate 80mg/ml Oral suspension
94789998	Medroxyprogesterone acetate 80mg/ml Oral suspension
95700998	Norethisterone 200mg/1ml solution for injection ampoules
97454998	NORETHISTERONE 200mg/1mL inj
97920998	MEDROXYPROGEST 150mg/1mL inj
97921998	MEDROXYPROGEST 50mg/mL inj
Read Codes	
61B..00	Depot contraceptive

61B..11	Depot contraception
61B1.00	Depot contraceptive given
61B1.11	Depo-provera injection given
61B2.00	Depot contraceptive repeated
61B3.00	Depot contraceptive-no problem
61B4.00	Depot contraceptive - problem
61B5.00	Depot contraception stopped
61BZ.00	Depot contraceptive NOS
Implant Progestogens	
Read Codes	
61K..00	Subcutaneous contraceptive
61KA.00	Insertion of subcutaneous contraceptive
61KB.00	Check of subcutaneous contraceptive
61KD.00	Subcutaneous contraceptive in situ
61KE.00	Subcut contrcptive implnt palp
61KZ.00	Subcutaneous contraceptive NOS
7G2AB00	Insertion of subcutaneous contraceptive
7G2H700	Removal of subcutaneous contraceptive
9m7..00	Contraceptive implant removal invitation
7G2AA00	Insertion of Norplant
7G2H500	Removal of Norplant
Gemscript	
81886998	ETONOGESTREL 68mg implant
90908998	Etonogestrel 68mg implant
90909998	ETONOGESTREL 68mg implant
92888998	LEVONORGESTREL 38mg implant
98222998	Levonorgestrel 228mg Implant
LNGIUSs	
Read	
615S.00	Mirena coil check
7E09500	Removal of Mirena coil
7E09400	Introduction of Mirena coil
Gemscript	
91324998	Levonorgestrel 20micrograms/24hours intrauterine device
91325998	LEVONORGESTREL 52mg i-u system

Table 16.3 ATC codes to identify treatment for acne in the year before index date in PHARMO and HSD

Substance	**ATC code***
Topicals	
Topical antibiotics	D10AF
Corticosteroids in topical combinations	D10AA
Topical retinoids	D10AD
Other topical preparations	D10AB, D10AE, D10AX, D01AE12
Systemic preparations	
Systemic retinoids	D10BA
Systemic antibiotics	J01AA08, J01AA07, J01AA02, J01FA01
Other systemic preparations	D10BX
Hormonal agents	
Hormonal contraceptives	G03A
Anti-androgens	G03H

NOTE: preliminary table, final codes will be selected based on local guidelines as described in section 9.3.

Table 16.4 Gemscript codes to identify treatment for acne in the year before index date in THIN

Gemscript	Descriptor
Topical solutions	
74977994	Generic aknicare lotion
74979994	Generic aknicare cream
74985994	Generic aknicare sr skin roller
81780998	Benzoyl peroxide 10% wash
81783998	Benzoyl peroxide 10% aq.gel
81814998	Benzoyl peroxide 5% gel
82355998	Benzoyl peroxide 10% gel
82356998	Benzoyl peroxide 5% gel
82430998	Adap 0.1% / ben perox 2.5% gel
82431998	Adapalene 0.1% / benzoyl peroxide 2.5% gel
82939978	Benzoyl perox+clind 3%/1% gel
82940978	Benzoyl peroxide 3% / clindamycin 1% gel
82985998	Nicotinamide 4% topical gel
85337998	Clindamycin 1% gel
85550998	Salicylic acid & sulphur cream
85606998	Azelaic acid 15% gel
85608998	Azelaic acid 15% gel
86859998	Nicotinamide 4% topical gel
87171998	Tretinoin with hydrocortisone and hydroquinone 0.1% + 1% + 5% cream
87527998	Benzoyl peroxide 5% / clindamycin 1% gel
87865998	Benz perox 5% / clindam 1% gel
87866998	Clindamycin 1% with benzoyl peroxide 5% gel
88057996	Chlorhexidine gluconate 1% solution
88087998	Erythromycin 4% topical gel
88090998	Erythromycin 2% topical gel
88921998	Benzoyl peroxide 10% lotion
88923998	Benzoyl peroxide 5% lotion
89203998	Nicotinamide 4% topical gel
89241997	Adapalene 0.1% cream
89241998	Adapalene 0.1% topical gel
89242997	Adapalene 0.1% cream
89242998	Adapalene 0.1% gel
89561998	Benz perox+pot hydrox sulf cream
90070998	Benz perox+pot hydrox sulf cream
90453997	Generic ddd medicated lotion
90564979	Azelaic acid 20% cream
90568998	Benzoyl peroxide 5% / erythromycin 3% gel
90794996	Benzoyl peroxide 10% / potassium hydroxyquinoline sulphate 0.5% cream
90794998	Benzoyl peroxide with potassium hydroxyquinoline sulphate 5% gel lotion
90839979	Adapalene 0.1% cream
90846979	Clindamycin 1% alcoholic solution

90852979	Clindamycin 1% roll-on lotion
90859979	Erythromycin 40mg/ml / zinc acetate 12mg/ml lotion
90861979	Erythromycin 40mg/ml / zinc acetate 12mg/ml lotion
90862979	Erythromycin 40mg/ml / zinc acetate 12mg/ml lotion
90863979	Erythromycin 40mg/ml / zinc acetate 12mg/ml lotion
90914998	Erythromy+tretin 4/0.025% solution
90915998	Tretinoin 0.025% / erythromycin 4% solution
91214998	Chlorhexidine 0.5% gel
91238998	Isotretin+erythro 0.05%/2% gel
91250998	Nicotinamide 4% gel
91251998	Nicotinamide 4% topical gel
91713998	Benzoyl peroxide 2.5% cream
91953998	Clindamycin 1% gel
91995997	Tretinoin 0.025% gel
91995998	Tretinoin 0.025% gel
92040998	Sulphur 8% with triclosan 0.1% cream
92041998	Sulphur 8% with triclosan 0.1% cream
92074996	Chlorhexidine glucon 0.5% gel
92074997	Chlorhex glucon 1% wash lotion
92074998	Chlorhexdne glucon 0.1% lotion
92284998	Clindamycin 1% gel
92483997	Benzoyl peroxide 2.5% cream
92483998	Benzoyl peroxide 4% cream
92484998	Benzoyl peroxide 4% cream
92525998	Chloramphenicol with hydrocortisone, nicotinate, allantoin with sulphur lotion
92660998	Erythromycin 3% topical gel
92669998	Benzoyl peroxide 5% with erythromycin 3% gel
93161998	Benzoyl peroxide 10% lotion
93222992	Clearasil max 10 cre
93225992	Benzyl peroxide cre 10 %
93234997	Tretinoin 0.025% cream
93234998	Tretinoin 0.01% gel
93235997	Tretinoin 0.025% gel
93235998	Tretinoin 0.025% lotion
93268998	Erythromycin 40mg/ml / zinc acetate 12mg/ml lotion
93303992	Sulphur comp oin
93304998	Erythromycin 40mg/ml / zinc acetate 12mg/ml lotion
93588992	Neutrogena acne soap
93633992	Benzoyl peroxide 10%/sulphur 5% % lot
93634992	Benzoyl peroxide 10%/sulphur 5% % cre
93635992	Benzoyl peroxide 5%/sulphur 2% % cre
93825992	Benzoyl peroxide 5% lotion
93864992	Dome-acne medicated cleanser gel
93899998	Tetracycline 2.2mg/ml topical solution

93959998	Chloramphenicol with hydrocortisone, nicotinate, allantoin with sulphur lotion
93960998	Topical corticosteroid preparation lotion
93969992	Resorcinol oin
93983992	Sulphur precipitated/resorcinol monoacet cre
94013998	Tretinoin 0.025% cream
94014996	Tretinoin 0.025% gel
94014997	Tretinoin 0.01% gel
94014998	Tretinoin 0.025% lotion
94177998	Polyethyl+benzalk cl gel
94178997	Aluminium oxide 52% paste
94178998	Aluminium oxide 38% paste
94339998	Benzoyl peroxide 5% with miconazole nitrate 2% cream
94340998	Benz peroxide+miconazole cream
94341998	Miconazole with benzoyl peroxide 2% with 5% cream
94422992	Benzoyl peroxide 10%/sulphur 2.5% % cream
94425992	Benzyl peroxide .5 % oin
94427992	Brasivol 3 paste pas
94461996	Benzoyl peroxide 10% wash
94461997	Benzoyl peroxide 10% cream
94461998	Benzoyl peroxide 10% gel
94555992	Theraderm 5 5 % gel
94587998	Erythromycin 2% lotion
94588996	Erythromycin 4% gel
94588997	Erythromycin 2% gel
94588998	Erythromycin 2% solution
94705992	Benoxyl 10 + sulphur lot
94706992	Benzoyl peroxide 5% cream
94713992	Benzoyl peroxide 5%/sulphur 2% % lot
94714992	Benzoyl peroxide 20 % lot
94781997	Clindamycin 1% roll-on lotion
94781998	Clindamycin 1% alcoholic solution
94782997	Clindamycin 1% aqueous lotion
94782998	Clindamycin 1% alcoholic solution
94837992	Clindamycin 1.5 % lot
95001998	Benzoyl peroxide 10% gel
95002998	Benzoyl peroxide 5% gel
95003997	Benzoyl peroxide 10% wash
95003998	Benzoyl peroxide 10% aq.gel
95004998	Benzoyl peroxide 5% aq.gel
95005998	Benzoyl peroxide 2.5% aq.gel
95007996	Benzoyl peroxide 10% alcohol based gel
95007997	Benzoyl peroxide 5% alcohol-based gel
95007998	Benzoyl peroxide 5% cream
95008996	Benzoyl peroxide 5% lotion

95008997	Benzoyl peroxide 5% gel
95008998	Benzoyl peroxide 2.5% gel
95230998	Sulphur & salicylic acid cream
95231998	Sulfur 8% / resorcinol 2% cream
95308992	Neo-medrone lot
95322998	Resorcinol 2% & sulphur 8% cream
95535992	Quinoderm lotio-gel 10 % lot
95628992	Sulphur/salicylic acid application liq
95629992	Sulphur precipitated/resorcinol monoacet lot
95965992	Benzoyl peroxide 10% lotion
95991992	Salicylic acid & sulphur paste pas
96152998	Hydrocortisone 1% / potassium hydroxyquinoline sulphate 0.5% cream
96375992	Oxy wash 10 % liq
96404992	Potassium hydroxyquinoline sulphate/benz 5 % lot
96429992	Tretinoin 0.025% lotion
96432992	Salic.acid /sulphur precip./emulsifying .25 % oin
96626994	Polyethyl+benzalk cl gel
96900992	Clindamycin phosphate roll-on 10 mg/ml lot
97121992	Chlorhexidine gluconate .5 % gel
97276998	Tetracycline 2.2mg/ml solutio
97283998	Benzoyl peroxide with hydrocortisone cream
97284996	Benz per+pot hydrox sul lotio
97284997	Benz perox+pot hydrox sulf crm
97284998	Benz perox+pot hydrox sul crm
97285998	Benzoyl peroxide 10% gel
97363998	Resorcinol acetate with sulphur cream
97382992	Erythromycin acne lotion 1 % lot
97453997	Benzoyl peroxide 10% gel
97453998	Benzoyl peroxide 5% gel
97685998	Salicylic acid 2% solution
97750998	Salicylic acid 2% solution
97838992	Benzoyl peroxide 5% lotion
97892992	Phisohex cre
97938992	Potassium hydroxyquinoline sulphate/benz .5 % cre
97977998	Sulphur 10% ointment
97978998	Sulphur comp 4% lotion
97979998	Salicylic acid 3% / sulfur 3% ointment
97980998	Salicylic acid 2% & sulphur 2% cream
97981998	Resorcinol and sulphur paste
98010992	Seba-med lotion lot
98011992	Seba-med crm cre
98012992	Sebamed cleansing bar
98186998	Isotretinoin 0.05% / erythromycin 2% gel
98199992	Tretinoin .02 % lot

98200992	Tretinoin .02 % gel
98568996	Benzoyl peroxide 5% lotion
98568997	Benzoyl peroxide 5% cream
98568998	Benzoyl peroxide 5% gel
98570998	Aluminium oxide 52% paste
98571998	Sulphur 5% with benzoyl peroxide 10% cream
98572998	Sulphur 2% with benzoyl peroxide 5% cream
98573998	Benzoyl peroxide 5% gel
98860998	Benzoyl peroxide 10% gel
99253998	Isotretinoin 0.05% gel
99258998	Isotretinoin 0.05% gel
99288997	Benzoyl peroxide 10% lotion
99288998	Benzoyl peroxide 10% gel
99321990	Salicylic acid 3% / sulfur 3% ointment
99658997	Benzoyl peroxide 5% aq.gel
99658998	Benzoyl peroxide 10% gel
99675998	Sulfur+resorcinol 8/2% cream
99744998	Azelaic acid 20% cream
99745998	Azelaic acid 20% cream
99784992	Acne-aid soap
99838992	Aluminium comp paste pas
99842992	Aluminium oxide medium paste 52.2 % pas
99843992	Aluminium oxide fine paste 38.09 % pas
99881998	Aluminium oxide 38% paste
99901998	Benzoyl peroxide 10% lotion
99902997	Benzoyl peroxide 5% lotion
99902998	Benzoyl peroxide 5% cream
99988998	Generic actinac lotion
99993998	Benzoyl peroxide 5% gel
99995998	Benzoyl peroxide 2.5% gel
Systemic preparations	
55596979	Lymecycline 408mg capsules
81719998	Minocycline 100mg m/r capsules
83064998	Erythromycin 500mg tablets
83065998	Erythromycin stear 500mg tabs
86390998	Minocycline 100mg m/r capsules
86753998	Minocycline 100mg m/r capsules
87959998	Minocycline 100mg m/r capsules
88431998	Doxycycline 100mg capsules
91308998	Minocycline 100mg tablets
91630998	Doxycycline 100mg dispersible tablets sugar free
92362998	Doxycycline 100mg capsules
92601997	Minocycline 100mg tablets
92601998	Minocycline 50mg tablets

92775990	Doxycycline 100mg capsules
92854997	Minocycline 100mg capsules
92854998	Minocycline 50mg capsules
92856998	Doxycycline 100mg capsules
92931998	Minocycline 50mg tablets
93484992	Doxycycline 100mg capsules
93923998	Doxycycline 100mg capsules
94147979	Erythromycin stear 500mg tabs
94148979	Erythromycin stear 500mg tabs
94151979	Erythromycin stear 500mg tabs
94159979	Erythromycin 500mg tablets
94819997	Erythromycin 500mg tablets
94820996	Erythromycin ethylsuccinate 500mg sachets
94820997	Erythromycin ethyl succinate 500mg tablets
94848990	Minocycline 100mg modified-release capsules
94933998	Lymecycline 408mg capsules
95369992	Oxytetracycline 500 mg tab
95801997	Minocycline 100mg tablets
95801998	Minocycline 50mg tablets
95991998	Lymecycline 408mg capsules
96089990	Doxycycline 100mg capsules
96282990	Doxycycline (as hyclate) 100mg tablets
96305996	Doxycycline (as hyclate) 100mg tablets
96305997	Doxycycline 100mg capsules
96305998	Doxycycline (as hyclate) 100mg dispersible tablets
96354990	Doxycycline 100mg capsules
96781997	Erythromycin stearate 500mg tablets
96785997	Erythromycin estolate 500mg tablets
97051990	Doxycycline 100mg capsules
97118997	Erythromycin 500mg ec gastro-resistant tablets
97121990	Doxycycline 100mg capsules
97209989	Doxycycline 100mg capsules
97246992	Doxycycline 100mg capsules
97361997	Erythromycin stear 500mg tabs
97381992	Erythromycin stear 500mg tabs
97559997	Minocycline 100mg tablets
97559998	Minocycline 50mg tablets
97738989	Minocycline 100mg tablets
97738990	Minocycline 50mg tablets
97761989	Doxycycline 100mg capsules
97913998	Doxycycline 100mg tablets
98029989	Minocycline 100mg tablets
98029990	Minocycline 50mg tablets
98044990	Doxycycline 100mg capsules

98166989	Erythromycin 500mg ec gastro-resistant tablets
98231998	Doxycycline 100mg disp tabs
98345990	Erythromycin 500mg ec gastro-resistant tablets
98352990	Doxycycline 100mg capsules
98480989	Minocycline 100mg tablets
98530998	Minocycline 100mg m/r capsules
98531996	Minocycline 100mg capsules
98531997	Minocycline 50mg capsules
98531998	Minocycline 100mg modified-release capsules
98558990	Erythromycin 500mg ec gastro-resistant tablets
98601989	Doxycycline 100mg capsules
98751997	Erythromycin 500mg/sach grans
98752998	Erythromycin 500mg e/c tablet
98754998	Erythromycin stear 500mg tabs
98969997	Doxycycline 100mg disp tabs
98969998	Doxycycline 100mg capsules
99054998	Lymecycline 408mg capsules
99101998	Doxycycline 100mg capsules
99103996	Erythromycin 500mg e/c tablet
99210990	Erythromycin 500mg ec gastro-resistant tablets
99433990	Erythromycin 500mg ec gastro-resistant tablets
99434990	Erythromycin 500mg ec gastro-resistant tablets
99435989	Erythromycin 500mg ec gastro-resistant tablets
99542997	Erythromycin stear 500mg tabs
99613990	Doxycycline 100mg capsules
99683997	Erythromycin 500mg e/c tablet

Table 16.5 Codes of diagnoses of hyperandrogenic conditions during the year before index date for PHARMO and HSD

Diagnosis*	**ICD-10**	**ICD-9(-CM)**	**ICPC**
Acne	L70	706.0, 706.1	S96
Alopecia	L63-L66	704.0	S23
Contraceptive management	Z30.01	V25.01, V25.02, V25.05	W11-W12
Hirsutism	L68.0	704.1,757.4 (incl. sub code 59 for HSD)	S24.01
Menstrual problems	N92, N94.3-N94.9	626.1, 626.2, 626.4, 626.8, 626.9	X02-X03, X06-X09
Oligomenorrhoea/amenorrhoea	N91	626.0, 626.1	X05
PCOS	E28.2	256.4	T99.06
Seborrhoea	L21	706.3	S86

*all diagnoses will be based on episode text mining in GP episodes as well; PCOS = polycystic ovary syndrome.

Table 16.6 Read codes of diagnoses of hyperandrogenic conditions or conditions EE/progestin combinations are prescribed for frequently during the year before index date for THIN

Read code	Descriptor
Acne	
2FG5.00	Acne scar
M153000	Acne rosacea
M26..00	Sebaceous gland diseases
M260.00	Acne varioliformis
M260000	Acne frontalis
M260z00	Acne varioliformis NOS
M261.00	Other acne
M261000	Acne vulgaris
M261100	Acne conglobata
M261600	Cystic acne
M261A00	Pustular acne
M261E00	Acne excoriee des jeunes filles
M261F00	Acne fulminans
M261X00	Acne, unspecified
M261z00	Other acne NOS
Myu6800	[X]Other acne
Myu6F00	[X]Acne, unspecified
Alopecia	
1N02.00	C/O: hair loss
22D4.00	O/E - loss of hair
22D7.11	O/E - alopecia
M240.00	Alopecia
M240000	Alopecia unspecified
M240011	Baldness
M240012	Hair loss
M240200	Male pattern alopecia
M240z00	Alopecia NOS
Contraceptive management	
61...00	Contraception
614..11	Oral contraception
614..12	Pill - oral contraception
6145.00	Oral contraception -no problem
614Z.00	Oral contraception NOS
61X..00	Planned contraception method
61Y..00	Uses contraception
61Z..00	Contraception NOS
6777.00	Contraception counselling
6147.00	Combined oral contraceptive

67Ij.00	Advice to GP to change pt oral contraceptive from combined
1561.00	H/O: oral contraceptive usage
1561000	H/O: progestogen only oral contraceptive usage
614..00	Oral contraceptive
614..11	Oral contraception
614..12	Pill - oral contraception
6141.00	Oral contraceptive started
6142.00	Oral contraceptive stopped
6143.00	Oral contraceptive re-started
6144.00	Oral contraceptive repeat
6145.00	Oral contraception -no problem
6146.00	Oral contraception - problem
6146100	Headache caused by oral contraceptive pill
6146200	Hypertension induced by oral contraceptive pill
6147.00	Combined oral contraceptive
6148.00	Progestagen only oral contraceptive
6148.11	Mini-pill: oral contraceptive
6148.13	Progestogen only oral contraceptive
6149.00	Oral contraceptive changed
614D.00	Oral contraceptive prescribed
614E.00	Oral contraceptive advice
614Z.00	Oral contraception NOS
61J0.00	Oral contraceptive pill contraindicated
679a.00	Education about missed dose of oral contraceptive
67IH.00	Advice about progestogen only oral contraceptive
1569.00	H/O: symptothermal method of contraception usage
156B.00	H/O: withdrawal contraception method usage
1P77.00	Reason for no contraception
612..00	Contraception not needed
612Z.00	Contraception not needed NOS
6146.00	Oral contraception - problem
614F.00	Emergency contraception advice
615..11	Coil contraception
615..12	IUD contraception
616..11	CAP contraception
616..12	Diaphragm contraception
617..11	Sheath contraception
618..00	Rhythm method contraception
619..00	Withdrawal contraception
61A..00	Post-coital contraception
61AZ.00	Post-coital contraception NOS

61B..11	Depot contraception
61B5.00	Depot contraception stopped
61C..11	Spermicide alone contraception
61E..00	Sympto-thermal contraception
61FZ.00	Post-coital contraception NOS
61J0.00	Oral contraceptive pill contraindicated
679a.00	Education about missed dose of oral contraceptive
67IH.00	Advice about progestogen only oral contraceptive
1569.00	H/O: symptothermal method of contraception usage
156B.00	H/O: withdrawal contraception method usage
612..00	Contraception not needed
612Z.00	Contraception not needed NOS
6146.00	Oral contraception - problem
614F.00	Emergency contraception advice
61H..00	Contraception: female sterilis
61J..00	Contraception contraindicated
61L..00	Contraception status unknown
61M..00	Emergency contraception
61P..00	No current contraception
61Q..00	Partner contraception
61R..00	Intrauterine system contraception
61S..00	Contraception method not decided
61V..00	Problem with contraception
679K500	Education for withdrawal contraception
67P2.00	Discussion about contraception injection
8CAw.00	Advice about long acting reversible contraception
8CAw100	Verbal advice about long acting reversible contraception
8CAw200	Written advice about long acting reversible contraception
8CED.00	Emergency contraception leaflet given
8CEE.00	Contraception leaflet given
8CEF.00	Intrauterine device contraception leaflet given
8CEG.00	Long acting reversible contraception leaflet given
961..11	FP1001 - contraception claim
98CA.00	GMS4 claim - contraception (non IUCD) signed
98CB.00	GMS4 claim - contraception (non IUCD) sent to HA
98CC.00	GMS4 claim - contraception (non IUCD) up to date
98CD.00	GMS4 claim - contraception (non IUCD) due
98CE.00	GMS4 claim - contraception (non IUCD) due next visit
98CF.00	GMS4 claim - contraception (non IUCD) cancelled
98CG.00	GMS4 claim - contraception (non IUCD) not claimed
98CH.00	GMS4 claim - contraception (non IUCD) forgot to claim

98CI.00	GMS4 claim - contraception (non IUCD) paid
98CJ.00	GMS4 claim - contraception (non IUCD) returned unpaid
98CK.00	GMS4 claim - contraception (IUCD) signed
98CL.00	GMS4 claim - contraception (IUCD) sent to HA
98CM.00	GMS4 claim - contraception (IUCD) due with new IUCD
98CN.00	GMS4 claim - contraception (IUCD) paid
SP03217	Contraception IUCD causing bleeding
ZV15700	[V]Personal history of contraception
Hirsutism	
M241.00	Hirsutism - hypertrichosis
M241.11	Polytrichia
M241100	Idiopathic hypertrichosis
M241200	Hypertrichosis lanuginosa (acquired)
M241400	Hypertrichosis partialis
M241500	Hypertrichosis universalis
M241600	Polytrichia
M241z00	Hypertrichosis NOS
Menstrual problems	
K584.00	Premenstrual tension syndrome
K584.11	Migraine - menstrual
1573.11	H/O: heavy periods
K592.00	Excessive or frequent menstruation
K592.11	Frequent menses
K592.12	Hypermenorrhoea
K592000	Menorrhagia
K592011	Heavy periods
K592100	Polymenorrhoea
K592111	Epimenorrhoea
K592z00	Excessive or frequent menstruation NOS
K593.00	Puberty bleeding
K593.11	Pubertal bleeding and menorrhagia
K595.00	Ovulation bleeding
K595.11	Intermenstrual bleeding - regular
K596.00	Metrorrhagia
K596.11	Intermenstrual bleeding - irregular
K598.00	Menometrorrhagia
K599.00	Mid-cycle bleeding
K59y.11	Metropathia haemorrhagica
K59yx00	Dysfunctional uterine haemorrhage NOS
K59yx11	Dysfunctional uterine bleeding
K59yy00	Functional uterine haemorrhage NOS

K59z.11	Break - through bleeding
1574.00	H/O: dysmenorrhoea
Eu45y11	[X]Psychogenic dysmenorrhoea
K582.00	Mittelschmerz - ovulation pain
K583.00	Dysmenorrhoea
K583.11	Painful menorrhoea
K583.12	Painful menstruation
K583.13	Period pains
K583.14	Spasmodic dysmenorrhoea
K583000	Primary dysmenorrhoea
K583100	Secondary dysmenorrhoea
1572.00	H/O: polymenorrhoea
158..00	H/O: abnormal uterine bleeding
158..12	Vaginal bleeding
K56y111	Bleeding - vaginal NOS
K56y112	BPV - Vaginal bleeding
K592.11	Frequent menses
K59y300	Intermenstrual bleeding
K594.00	Irregular menstrual cycle
K594000	Delayed period
K594011	Late period
K594z00	Irregular menstrual cycle NOS
1573.00	H/O: menorrhagia
K5A0.00	Premenopausal menorrhagia
K5A0.11	Climacteric menorrhagia
K5A6.00	Perimenopausal menorrhagia
158..00	H/O: abnormal uterine bleeding
1584.00	Heavy episode of vaginal bleeding
K592.00	Excessive or frequent menstruation
K592z00	Excessive or frequent menstruation NOS
K59y.00	Other menstruation disorders
K59yz00	Other menstruation disorder NOS
K592000	Menorrhagia
K59y000	Retained menstruation
K594012	Delayed menstruation
Oligomenorrhoea/amenorrhoea	
1571.00	H/O: amenorrhoea
K590.00	Absence of menstruation
K590.11	Amenorrhoea
K590000	Primary amenorrhoea
K590100	Secondary amenorrhoea
K590111	Post-pill amenorrhoea

K590z00	Amenorrhoea NOS
K591.00	Scanty or infrequent menstruation
K591.11	Infrequent menstruation
K59y100	Suppression of menstruation
1571.00	H/O: amenorrhoea
K590.00	Absence of menstruation
K590111	Post-pill amenorrhoea
K591000	Hypomenorrhoea
K591100	Oligomenorrhoea
K591200	Primary oligomenorrhoea
K591300	Secondary oligomenorrhoea
K591z00	Scanty or infrequent menstruation NOS
PCOS	
C164.00	Polycystic ovaries
C164.11	Isosexual virilisation
C164.12	Stein - Leventhal syndrome
C164.13	Multicystic ovaries
C165.00	Polycystic ovarian syndrome
C16y.00	Other ovarian dysfunction
Seborrhoea	
M263.00	Seborrhoea
M263000	Seborrhoea corporis
M263100	Seborrhoea faciei
M263200	Seborrhoea nasi
M263300	Seborrhoea oleosa
M263z00	Seborrhoea NOS
M263z00	[X]Other seborrheic dermatitis

17. Annex 4. ENCePP checklist

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:

Study reference number:

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☒	☐	☐	7
1.1.4 Interim progress report(s)	☒	☐	☐	7
1.1.5 Registration in the EU PAS register	☒	☐	☐	7
1.1.6 Final report of study results.	☒	☐	☐	7

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7,8
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	9
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	9
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

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

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	11-13
4.2 Is the planned study population defined in terms of:	☒	☐	☐	9
4.2.1 Study time period?	☒	☐	☐	9
4.2.2 Age and sex?	☒	☐	☐	6
4.2.3 Country of origin?	☒	☐	☐	9
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?				
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☐	☒	☐	
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☒	☐	

Comments:

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity,	☐	☐	☒	

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)				

Comments:

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	11-13
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☐	☐	☒	
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	11-13
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	11-13
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	11-13
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	39-45
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☐	☒	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☒	☐	☐	28-39
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	14
10.3 Are descriptive analyses included?	☒	☐	☐	14
10.4 Are stratified analyses included?	☒	☐	☐	14
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	13-14
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	13-14
11.3 Are methods of quality assurance described?	☒	☐	☐	13-14
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	13-14
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	13-14

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss: 12.1.1 Selection biases?	☒	☐	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	15
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	13
12.3 Does the protocol address other limitations?	☒	☐	☐	15

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	7
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	15,16

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	7

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	17
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	17

Comments:

Name of the main author of the protocol: _____

Date: / /

Signature Page – European Qualified Person for Pharmacovigilance (EU QPPV)

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
IMPACT study number	
Study type	☐ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Project team member at Bayer AG
Name	Dr. Michael Kayser
Title	EU QPPV
Address	Bayer AG , **Qualified Person for Pharmacovigilance** BPH-GMAPV-QPPV Building: 0470, 412 Office: 412 Wuppertal Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 17.05.2017

Gerhard Reike, Deputy QPPV-EU

Signature Page – Global Safety Physician

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
IMPACT study number	
Study type	☒ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Pharmacovigilance Risk Management
Name	Dr. Kerstin Gude
Title	Global Safety Lead
Address	Bayer AG , Müllerstraße 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 16-MAY-2017,

Signature Page – Principal Investigator HSD

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	12 May 2017
IMPACT study number	
Study type	☒ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Principal Investigator
Name	Francesco Lapi
Title	PharmD, PhD
Address	Health Search, Italian College of General Practitioners and Primary Care (at Genomedics S.R.L.), Sestese 61, 50141, Florence, Italy

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 11 May 2017, 

Signature Page – Principal Investigator THIN

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
IMPACT study number	
Study type	☒ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Principal Investigator
Name	Luis Alberto García Rodríguez
Title	MD, MSc, Director
Address	The Health Improvement Network / Centro Español de Investigación Farmacoepidemiológica, Almirante 28, 2, 28004, Madrid, Spain

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature:  ,

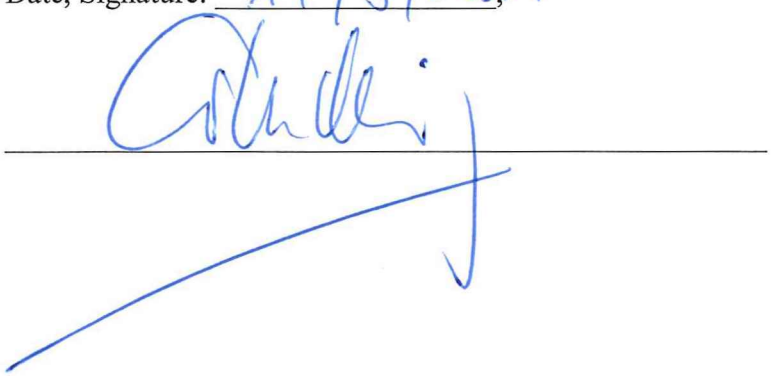
12 May 2017

Signature Page – Medical Affairs

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
IMPACT study number	
Study type	☒ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Medical Affairs
Name	Dr. Christiane von Ludwig
Title	Medical Affairs Physician
Address	Bayer AG , Müllerstraße 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 17/5/2017



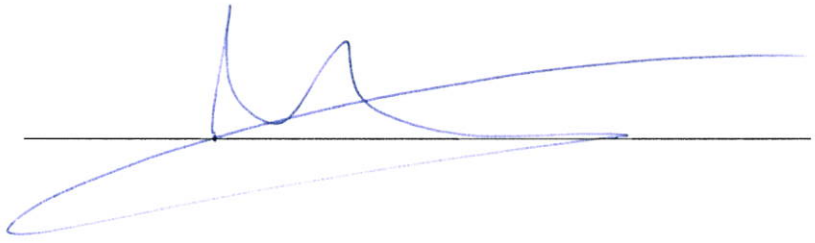
1. Annex 5. Signature pages

Signature Page – Principal Investigator PHARMO

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
IMPACT study number	
Study type	☒ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Principal Investigator
Name	Irene Bezemer
Title	PhD, International Research Program Manager
Address	PHARMO Institute for Drug Outcomes Research, Utrecht, The Netherlands

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature: 15-05-2017,



Signature Page – Statistics

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
IMPACT study number	
Study type	☒ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Statistics
Name	Dr. Christoph Gerlinger
Title	Senior Director, Expert Statistician
Address	Bayer AG , Müllerstraße 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

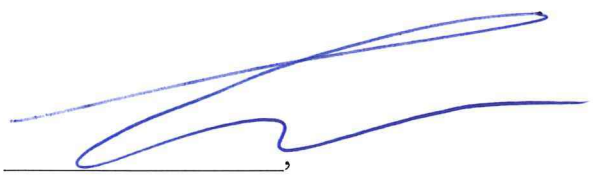
Date, Signature: 22 MAY 2017,

GeL

Signature Page – Study Responsible/ Epidemiology

Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Protocol version identifier	Version 7.0
Date of last version of protocol	19 March 2015
IMPACT study number	
Study type	☒ PASS ☐ non PASS
EU PAS register number	EUPAS8412
Active substance (medicinal product)	Cyproterone/ethinylestradiol (CPA/EE), ATC code G03HB01, Antiandrogens and estrogens
Marketing authorization holder(s)	Bayer AG on behalf of a group of MAHs
Function	Epidemiology
Name	Dr. Alex Asiimwe
Title	Epidemiology
Address	Bayer AG , Müllerstraße 178, 13353 Berlin, Germany

The undersigned confirms that the study will be conducted in compliance with the protocol and any applicable regulatory requirements.

Date, Signature:  ,

11. MAY 2017.