Title	Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	Not applicable, this is the first version
EU PAS register number	ENCEPP/SDPP/8412
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 authorized products and/or, if possible, of nationally authorised products subject to the study
Procedure number	Referral: EMEA/H/A-107i/1357
Marketing authorisation holder(s)	Bayer Pharma 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, recent diagnosis of acne, hirsutism or other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management, recent acne treatment and (concomitant) use of hormonal contraceptives in three European databases, i.e. PHARMO, THIN and HSD. A secondary objective is to compare user and treatment characteristics between 01 January 2011 and 31 December 2012 and 01 January 2014 and 31 December 2014.
Country(-ies) of study	Netherlands, United Kingdom, Italy
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The study was 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.

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1 Abstract

Title

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

Keywords

Cyproterone/ethinylestradiol, hormonal contraceptives, acne, treatment patterns

Rationale and background

Cyproterone acetate in combination with ethinylestradiol (CPA/EE) is indicated for the treatment of moderate to severe acne when topical therapy or systemic antibiotic treatments have failed, and for hirsutism in women of reproductive age. In 2013 MAHs were required to implement further risk minimization measures.

Research question and objectives

This study aimed to assess recent diagnosis of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management, recent acne treatment and concomitant use of other hormonal contraceptives (HC) among new users of CPA/EE in 2011 and 2012 and in 2014 for comparison between the study periods.

Study design

In this retrospective drug utilization study, new CPA/EE users in 2011, 2012 and 2014 were followed from their first CPA/EE prescription until database exit or end of index year (31 December 2011 or 31 December 2012 or 31 December 2014).

Setting

CPA/EE prescriptions were identified in the PHARMO Out-patient Pharmacy Database (the Netherlands), the Health Search Database (HSD, Italy) and The Health Improvement Network (THIN, United Kingdom).

Subjects and study size, including dropouts

The study population included 11,131 new CPA/EE users in 2011, 10,931 new users in 2012 and 4,003 new users in 2014.

Variables and data sources

Type and prescriber (PHARMO only) of the first CPA/EE prescription and diagnoses of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management and treatment of acne in the preceding year were assessed. During follow-up, the duration of CPA/EE use, concomitant use of CPA/EE and other HC and duration of concomitant use were assessed.

Results

In PHARMO, the number of new CPA/EE users identified per year was 7,876 in 2011, 7,562 in 2012 and 1,401 in 2014. The proportions of new users in the source population were 2.8, 2.6 and 0.7 per 1,000 women, respectively. GP data to assess diagnoses in new CPAEE users was available for about 20% of the population. The diagnoses among new CPA/EE users in the PHARMO database were studied using this sub-cohort. A recent acne diagnosis was observed in 17%, 16% and 12% of new CPA/EE users, respectively. Among users with no acne diagnosis, 40-45% had recently received acne treatment so in total 55% of users in 2011, 52% of users in 2012 and 47% of users in 2014 had a recent record of acne diagnosis or treatment. A diagnosis of hyperandrogenic conditions other than acne was observed for 3-4% in all study years. Of the CPA/EE users without any hyperandrogenic diagnosis, 3% had menstrual problems and another 12-15% had an entry for contraceptive management. Concomitant use of other HC was observed for 3% of new CPA/EE users in 2011, and 2% in 2012 and 2014 (median duration 78 days in all study years). Another 25% were potential concomitant users (median duration about 60 days).

In THIN, the number of new CPA/EE users identified per year was 2,760 in 2011, 2,923 in 2012 and 2,341 in 2014. The proportions of new users in the source population were 1.6, 1.6 and 1.3 per 1,000 women, respectively. A recent acne diagnosis was observed in 51%, 54% and 55% of new CPA/EE users, respectively. Among users with no acne diagnosis, 50-54% had recently received acne treatment so in total 76% of users in 2011, 79% of users in 2012 and 78% of users in 2014 had a recent record of acne diagnosis or treatment. A diagnosis of hyperandrogenic conditions other than acne was observed for 8-9% of users in all study years. Of the CPA/EE users without any hyperandrogenic diagnosis, 4-5% had menstrual problems and another 20-23% had an entry for contraceptive management. Concomitant use of other HC was observed for 1% of new CPA/EE users in 2011 and less than 0.5% in 2012 and 2014 (median duration 84 days in 2011 and 2012 and 77 days in 2014). Another 4-5% were potential concomitant users (median duration 50 days in 2011 and 2012 and 34 days in 2014).

In HSD, the number of new CPA/EE users identified per year was 495 in 2011, 446 in 2012 and 261 in 2014. The proportions of new users in the source population were 0.8, 0.8 and 0.5 per 1,000 women, respectively. A recent acne diagnosis was observed in 14%, 17% and 14%

of new CPA/EE users, respectively. Among users with no acne diagnosis, 5-6% had recently received acne treatment so in total 19% of users in 2011, 21% of users in 2012 and 18% of users in 2014 had a recent record of acne diagnosis or treatment. A diagnosis of hyperandrogenic conditions other than acne was observed for 7-10% of users in all study years. Of the CPA/EE users without any hyperandrogenic diagnosis, 5-6% had menstrual problems and another 7-11% had an entry for contraceptive management. Concomitant use of other HC was observed for 1% of new CPA/EE users in 2011 and 2012 and 2% of new CPA/EE users in 2014. The absolute number of concomitant users was too low to report summary statistics about concomitant use. Another 2-4% were potential concomitant users (median duration about 28-29 days in 2011 and 2012, not reported in 2014 (<5 users)).

Discussion

The overall prescription of CPA/EE decreased noticeable between 2011 and 2014 in PHARMO and HSD, and slightly in THIN. More than 70% of the new CPA/EE users in THIN, about half of the new CPA/EE users in PHARMO, and the minority of users in HSD had a recent record of acne diagnosis or treatment. In all three databases, up to 10% of users had diagnoses of other hyperandrogenic conditions. GP consultations for contraceptive management were observed for part of the users without hyperandrogenic diagnoses. It should be noted that information about on-label diagnoses might have been missing due to underreporting in the databases. Concomitant use of other HC was observed for up to 3% of new CPA/EE users across the databases. Additionally, potential concomitant users of other HC were observed. However, as no new prescription was observed after the start of potential concomitant use, an actual switch was likely for these users.

The key difference observed between the study periods before and after the referral procedure was the overall reduction in CPA/EE use.

Marketing Authorisation Holder(s)

Bayer Pharma AG on behalf of a group of MAHs.

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2 List of abbreviations

AG	Aktiengesellschaft
ANSM	Agence Nationale de Sécurité du Médicament et des Produits de Santé
ATC	Anatomical Therapeutic Chemical (classification system)
CPA	Cyproterone Acetate
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedures – Human
DUS	Drug Utilization Study
EE	Ethinylestradiol
EMA	European Medicines Agency
EU	European Union
GP	General Practitioner
HC	Hormonal Contraceptives
HSD	Health Search Database
ICD	International Classification of Diseases
ICPC	International Classification of Primary Care
IQR	Interquartile Range
LARC	Long-Acting Reversible HC
MAH	Marketing Authorization Holder
n.a.	Not applicable
PCOS	Polycystic Ovary Syndrome
PRAC	Pharmacovigilance Risk Assessment Committee
SAS	Statistical Analysis System
SD	Standard Deviation
SQL	Structured Query Language
THIN	The Health Improvement Network
UK	United Kingdom
WHO	World Health Organization

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5 Milestones

Regulatory submission of the Study Protocol for the database Drug Utilization Study was done in September 2014. A progress (interim) report containing 2011 and 2012 results was delivered in Q3 2015.

The data of 2014 for the three databases (PHARMO, THIN, HSD) became available mid-2015. Separate study reports were delivered for each database in December 2015 and subsequently compiled in one document. Currently planned dates for deliverables are indicated in Table 5.1.

Table 5.1 Milestones and deliverables

Milestone[a]	Planned date	Actual date	Comments
Start of data collection	January 2015	January 2015	This is the date of start of extractions. Data are collected retrospectively.
End of data collection	January 2016	January 2016	This is the date of end of extractions. Data are collected retrospectively and up to 31 December 2014.
Registration in the EU PAS register	January 2015	January 2015	-
Progress (interim) report to PRAC	Q3 2015	August 2015	-
Final report of study results	March 2016	-	-

6 Rationale and background

Cyproterone acetate (CPA) 2mg, in combination with ethinylestradiol (EE) 35mcg (CPA/EE) is a medicinal product currently indicated for the treatment of moderate to severe acne and/or hirsutism in women of reproductive age. Androgen-dependent conditions such as acne, hirsutism, seborrhoea, and androgenic 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. Marketing authorization was first granted in 1985 in Germany.

CPA/EE was the subject of a European Article 107i Urgent Union Procedure instigated by the French Medicine Agency, ANSM, in February 2013 to investigate CPA/EE safety in its users. 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 systemic antibiotic treatment, have failed.

Since CPA/EE also acts as a hormonal contraceptive (HC), women should not take this medicine in combination with other HC. The concomitant use of CPA/EE with other HC 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 users highlighting the risks of thromboembolism (1) and to conduct drug utilization and post authorisation safety studies.

This document presents the 2011, 2012 and 2014 results of a drug utilization study (DUS) on the use of CPA/EE in three European countries. The aim of this drug utilization study is to compare the user characteristics of 2011 and 2012 with 2014, i.e. before and after the PRAC recommendation. 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.

7 Research question and objectives

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

- User demographics
- Treatment characteristics
- Recent diagnosis of acne, hirsutism, other hyperandrogenic conditions, menstrual problems or general practitioner (GP) consultations for contraceptive management
- Recent acne treatment
- (Concomitant) use of hormonal contraceptives (HC)

A secondary objective is:

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

The current report describes the analysis on the 2011 and 2012 data and on the 2014 data separately, and compares the results between the study periods.

8 Amendments and updates

Significant deviations from the Study Protocol that were implemented during data analysis are documented as such and the rationale provided.

Table 8.1 Deviations from 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.

Table 8.1 Deviations from the Study Protocol

Number	Date	Section of Study Protocol	Amendment or update	Reason
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.

9 Research methods

9.1 Study design

This is a retrospective cohort study in which CPA/EE users are selected from population-based healthcare databases. The PHARMO, THIN and HSD databases capture data from primary care, where diagnosis and treatment of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management as well as utilization of HC are captured. Moreover, all three databases are based in countries where the GP has a gatekeeper role.

9.2 Setting

The study population includes individuals registered in the databases receiving CPA/EE (ATC G03HB01 in PHARMO and HSD or Gemscript codes 85864998, 86466998, 86925998, 87351998, 90826979, 91068998, 91069998, 94832990, 94913992, 94920998, 95396990, 96577998 and 97520998 in THIN). CPA/EE prescriptions were identified as dispensings in the PHARMO Out-patient Pharmacy Database and as prescriptions in the HSD and THIN

databases. Throughout this report, the term ‘prescription’ refers to ‘dispensing’ for the PHARMO data.

9.3 Subjects

The study populations include all individuals who were prescribed CPA/EE between 01 January 2011 and 31 December 2012 (2011 and 2012 populations) and those who were prescribed CPA/EE between 01 January 2014 and 31 December 2014 (2014 population). Users were selected by calendar year (2011, 2012 and 2014) and were analysed separately. The date of receiving the first prescription of CPA/EE in the study period was defined as the index date.

Exclusion criteria were:

- 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 8.1 deviation #3) or
    - expiration of a prescription of CPA/EE in the year prior to index date (PHARMO only, see Table 8.1 deviation #1)

Users were followed from index date to transfer out of the database (end of follow-up available/censoring) or end of study period, whichever occurred first. The end of the study period was defined as December 31 of the year of index date (31 December 2011 for users starting in 2011, 31 December 2012, for users starting in 2012 and 31 December 2014, for users starting in 2014).

9.4 Variables

9.4.1 Descriptive data

The following demographic characteristics were assessed in the study population:

- Age at index date (in years, categorized, mean (± SD), median (IQR))
- Database history available prior to the index date (in years, categorized, mean (± SD), median (IQR))

- Database follow-up available after the index date (in months, categorized, mean (± SD), median (IQR))

9.4.2 Outcome data

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

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

NOTE: Distinction between prescriber was only relevant 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 were 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 CPA/EE and other HC (concomitant, potential concomitant, non-concomitant or no use of other HC
- Duration of concomitant use of CPA/EE and other HC (⩽28 days, >28 - 84 days or >84 days, mean (± SD) and median (IQR))
- Duration of potential concomitant use of CPA/EE and other HC (⩽28 days, >28 - 84 days or >84 days, mean (± SD) and median (IQR))

Prior diagnoses of acne or other hyperandrogenic conditions (on-label and potential on-label diagnoses), menstrual problems or GP consultations for contraceptive management in the absence of any of the hyperandrogenic conditions (potential off-label diagnoses) were assessed in the year prior to the index date (index date – 365 days, including the index date; for included codes, see Annex Table 5 and Annex Table 6:

- Any hyperandrogenic condition
    - Acne
    - Alopecia
    - Seborrhoea
    - Hirsutism
    - PCOS
- Menstrual problems in the absence of any of the hyperandrogenic conditions above
    - Menstrual disorder

    - Oligomenorrhoea/amenorrhoea
- Contraceptive management in the absence of any of the hyperandrogenic conditions or menstrual problems above

In PHARMO, CPA/EE users were selected from the Out-patient Pharmacy Database, but diagnoses of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management are captured in the GP Database. For the analyses of these conditions a subpopulation was created of users for whom data records were available from the GP Database.

Prior treatment of acne, according to European treatment guidelines (2), was assessed in the year prior to the index date (index date – 365 days, excluding index date; for included product names and ATC codes see Annex Table 3 and Annex Table 4). Acne treatments were classified as topicals, systemic preparations and hormonal agents and assessed separately for users with and without 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 was 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 were further classified to whether it is only approved for acne, or also approved for other indications to allow future sensitivity analysis.

9.4.3 Exposure

Prescriptions of CPA/EE from index date until end of follow-up were converted into treatment episodes of uninterrupted use (see section 9.4.3.1). To analyse concomitant use of CPA/EE and other HC, we collected information on HC up to five year preceding the index date until end of follow-up. ATC and Gemscript codes of HC are displayed in Annex Table 1 and Annex Table 2.

Treatment episodes of CPA/EE as well as other HC were created from prescriptions just before and during study follow-up. Because the discontinuation or removal dates were not captured in the prescription records, the end date of a prescription was based on the amount prescribed, or the life cycle for a long-acting reversible HC (LARC). The duration was determined per product in PHARMO. In PHARMO and HSD, treatment episodes were created from prescriptions *ending* on or after 01 January of the year before the study period (2010 for the 2011 and 2012 analysis and 2013 for the 2014 analysis) and *starting* before or on end of the study period. In THIN, treatment episodes were created from prescriptions *ending* from three months before the index date until end of follow-up for 28 days cycle HC and from prescriptions *starting* a time window representing the respective life cycle for each

long-acting reversible HC (LARC) of the index date. The time window was 3 years for implants, 5 years for intra-uterine devices, and 3 months for injections. In THIN removal of LARCs are recorded, within each time window we also looked for removal codes.

Subsequently, overlap between CPA/EE and other HC episodes was assessed and classified into non- concomitant, potential concomitant and concomitant use episodes as described in section 9.4.3.2.

9.4.3.1 Episodes of CPA/EE and other HC use

For all databases, the duration of each CPA/EE and other HC prescription included 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 was thus defined as 28 days and the duration of a prescription was the duration of one blister pack multiplied by the number of blister packs prescribed (see Figure 9.4.3.1.1). Each box in the Figure indicates one cycle, e.g. a blister pack. Subsequent cycles constitute a prescription, and subsequent prescriptions constitute a treatment episode.

Most (if not all) other oral HC, 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 was defined as the duration of effectiveness or until removal of the intra-uterine devices or implant when this was identified in the database. For each HC the duration of effectiveness was defined from the label.

Subsequent prescriptions of the same drug were concatenated if the new prescription date preceded the end date of the previous prescription. The adjusted start date of the new prescription was the day after the end date of the previous prescription. Subsequently, prescriptions of CPA/EE and other HC were converted into treatment episodes of uninterrupted use. In case of an interruption between two prescriptions, use of the drug was considered interrupted and the treatment episode ended, i.e. no gap was allowed between two prescriptions.

Users could have several treatment episodes of CPA/EE and other HC after treatment onset.

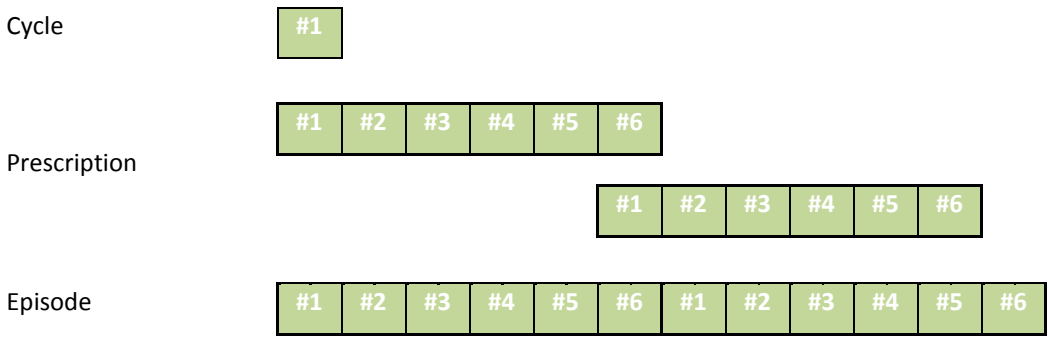

Figure 9.4.3.1.1 Cycles, prescriptions and treatment episodes of CPA/EE and other HC

9.4.3.2 Definition of switching and concomitant use of CPA/EE and other HC

Switching between HC was defined as a prescription date of a new HC preceding the end date of a previous episode of another HC. As most HC are given in cycles, the assumption was that the user finished a cycle (e.g. the blister pack or patch) of the first HC before starting a new one. Hence, the adjusted end date of the previous episode was the end date of the cycle during which the new prescription was observed. The adjusted start date of the new HC was the day after the adjusted end date of the previous HC.

If the previous contraceptive was not given in cycles (e.g. LARCs) the adjusted end date was set on the day before the date of the new prescription and the start date of the new HC was not adjusted.

For all episodes of CPA/EE, overlap with other HC episodes was assessed similarly to the switches between HC. However, as concomitant use of CPA/EE and other HC was among the study objectives, we did not define a switch but classified in terms of (potential) concomitant use:

- Potential concomitant use: (see Figure 9.4.3.2.1) when a "switch" from CPA/EE to another HC *or vice versa* occurs during the last prescription within a treatment episode
- Concomitant use: when both start and end date of a HC episode lie between start and end date of a CPA/EE episode *or vice versa*; or when a "switch" from CPA/EE to another HC *or vice versa* precedes the last prescription within a treatment episode**.**
- Non-concomitant use: both start and end date of a HC 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 other HC (no observed treatment episodes of other HC 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 was also computed separately for 28 days cycle HC (combined oral contraceptive pill, progestogen-only pill, patches, ring) and for LARCs (intra-uterine devices, implants and injections).

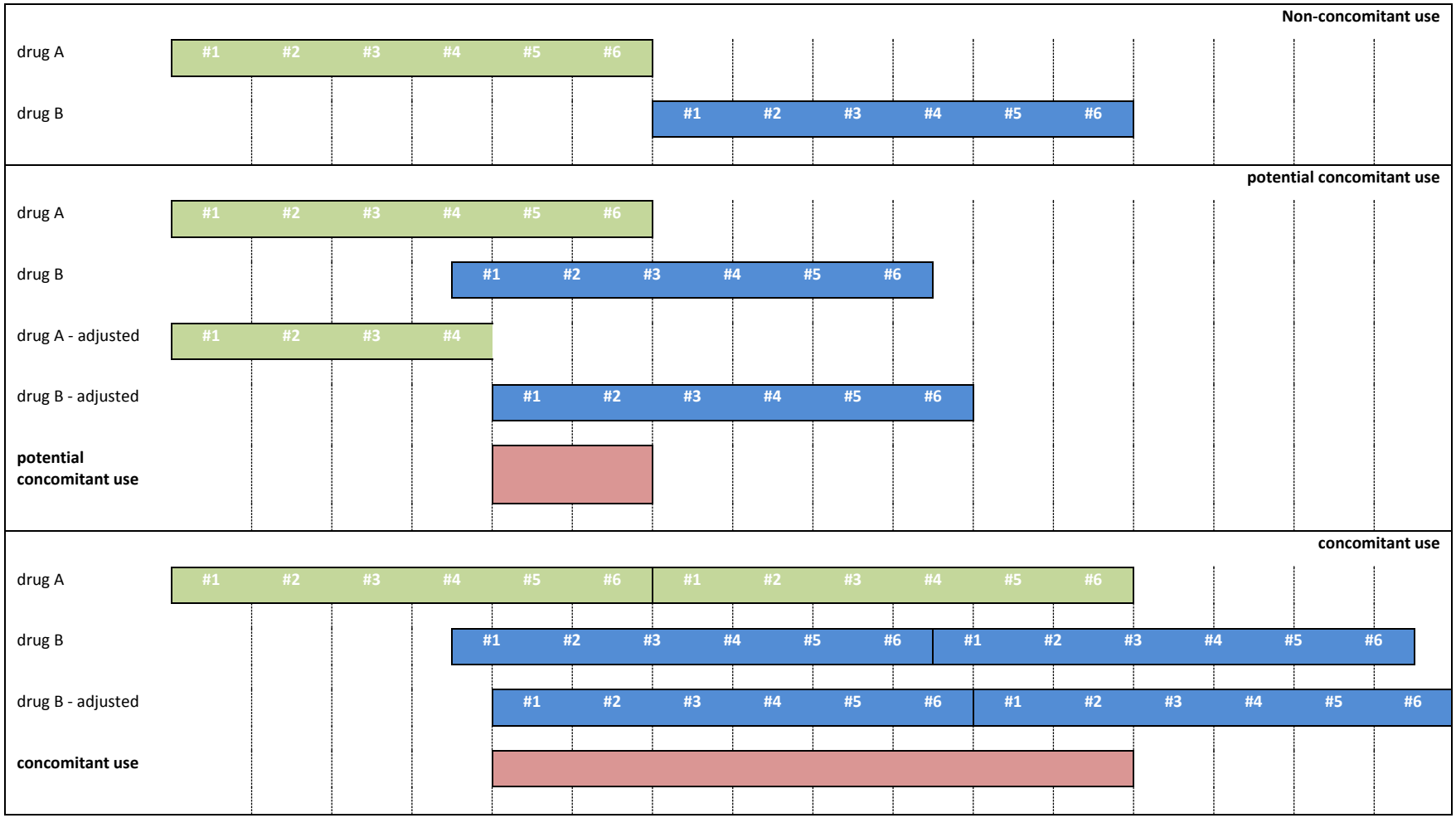

Figure 9.4.3.2.1 Definition of non-concomitant, potential concomitant and concomitant use of CPA/EE and other HC

9.5 Data sources and measurement

The study was 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'.

9.5.1 PHARMO Database Network - The Netherlands

The PHARMO Database Network includes several linked databases which contain data on user demographics, mortality, drug dispensings, hospital morbidity, laboratory, pathology and general practitioner information from 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 was best suited to identify diagnoses of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management. The Out-patient Pharmacy Database was used as a data source for identification of dispensings of CPA/EE, HC and acne medication as the GP is not directly involved in refill dispensings.

User demographics, treatment characteristics and concomitant use of HC were studied in the Out-patient Pharmacy Database population. Current size of this source population is 3.8 million.

Diagnoses of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management and recent acne treatment (by presence or absence of acne diagnosis) were studied in the overlapping population between the Out-patient Pharmacy Database and the GP Database. Current size of the overlapping population is ca. 0.8 million.

The PHARMO Database Network has already been used for several studies in the field of HC. Throughout this report, "prescription" refers to "dispensing" for the PHARMO data.

General Practitioner 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 prescription records include information on type of product, date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are coded according to the WHO ATC

Classification System (3). Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) (4), which can be mapped to ICD codes, but can also be entered as free text. GP data covered a catchment area representing 1.9 million residents for the interim analysis (2011 and 2012) and 2.5 million residents in the final analysis (2014).

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 ATC Classification System (3). Out-patient pharmacy data covered a catchment area representing 3.6 million residents for the interim analysis (2011 and 2012) and 3.8 million residents in the final analysis (2014).

9.5.2 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 HC 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 (5). The database has already been used for drug utilization studies on contraceptive methods (6-9). 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 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.

9.5.3 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 700 GPs from all Italian regions, covering a population of ca. 1.5 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, HC 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 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 HC 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, HSD is the only data source to possess it in Italy.

9.6 Bias

This study is a descriptive study without formal comparisons. Between the study periods, selection bias may apply when the proportions of CPA/EE prescribed in primary and secondary care changed in THIN and HSD. The user populations captured in the databases may then be not longer comparable. This is however unlikely due to the short time between the periods. Information bias could occur due to different degrees of underreporting in the study years.

9.7 Study size

In a preliminary analysis on the 2011 and 2012 data during protocol writing 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.

9.8 Data transformation

9.8.1 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.

9.8.2 The Health Improvement Network (THIN) – United Kingdom

The Health Improvement Network (THIN) database is provided by IMS Information Solutions Medical Research Ltd. THIN data are collected from participating Vision practices during routine GP consultations and regularly collated in THIN data. THIN data collection scheme started in 2003 and is approved by the UK National Health Service Research Ethics Committee (reference number: 07H1102103). THIN data currently contains the electronic medical records of almost 8 million UK patients (ca. 4 million active patients) collected from over 386 general practices in the UK covering more than 5.7% of the population in the UK (10). 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 THIN Additional Information Service 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.

9.8.3 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.

9.9 Statistical methods

Results on groups with less than 5 individuals are not reported in order to protect the confidentiality and privacy of the individuals.

9.9.1 Main summary measures

User, treatment and diagnosis characteristics are reported descriptively. Categorical data are presented as counts (n) and proportions (%). Continuous data are presented as means with standard deviation (SD) and as medians with interquartile range (IQR) when appropriate. Results are presented stratified by year of index date.

9.9.2 Main statistical methods

This is a descriptive study with summary measures only.

9.9.3 Missing values

Missing information about exposure or recent diagnoses and treatment is addressed in the limitation section of the discussion. No adjustment or sensitivity analysis was performed.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

Standard operating procedures at each research centre were 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 was reviewed independently by a senior researcher. All key study documents, such as the statistical analysis plan and study reports, underwent quality control and senior scientific review.

10 Results

10.1 Participants

10.1.1 PHARMO participants

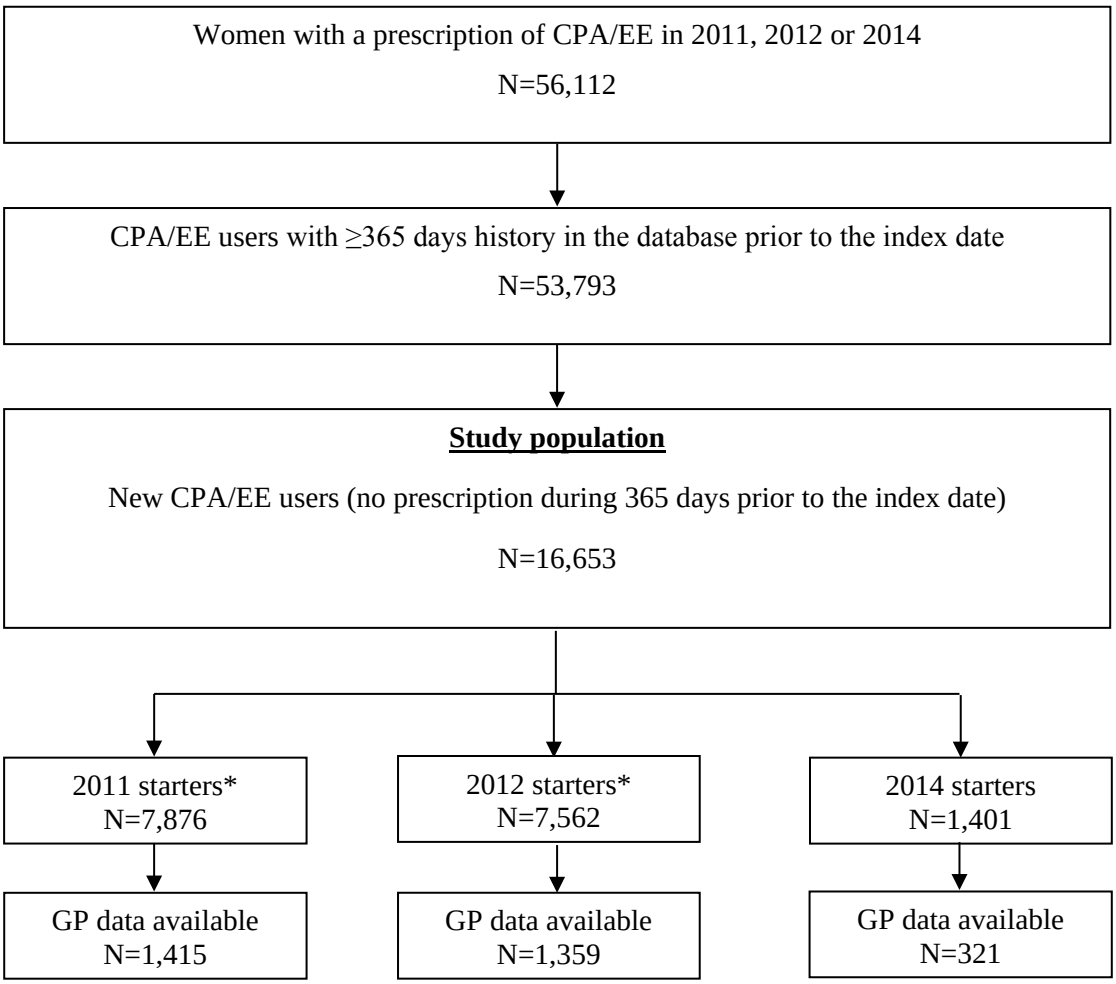

Figure 10.1.1.1 Flow chart of user selection in PHARMO

**Note: 186 users who were new users in 2011 as well as in 2012, i.e. stopped using CPA/EE in 2011 and re-started after more than 365 days in 2012, were included in both populations.*

All women with a prescription of CPA/EE in 2011, 2012 or 2014 were selected from the PHARMO Out-patient Pharmacy Database (Figure 10.1.1.1) Users with less than 365 days history in the database prior to the index date (N=2,319 (4%)) were excluded from the initial user population.

The overall user population, i.e. including prevalent users, was 35,637 in 2011, 34,403 in 2012 and 10,534 in 2014 (these are the total of 53,793 prevalent users across the study periods in Figure 10.1.1.1). The proportions of new users among women with at least 365 days history in the database were 2.8 per 1,000 women in 2011, 2.6 per 1,000 women in 2012 and 0.7 per 1,000 women in 2014.

For the final study population of new CPA/EE users, 37,140 (69%) prevalent users, i.e. who had used CPA/EE during the year before the index date, were excluded. The final study population of new CPA/EE users included 15,252 new users of CPA/EE in 2011 and 2012 (some of whom were included in both study years, see below), and 1,401 new users in 2014. The date of receiving the first prescription of CPA/EE in 2011, 2012 or 2014 was defined as the index date.

Three study populations were created for the study: new users in 2011, new users in 2012 and new users in 2014. Users who were new users in 2011 as well as in 2012, i.e. stopped using CPA/EE in 2011 and re-started after more than 365 days in 2012, were included in both populations (N=186 (2%) 2012 users). The number of users who were included in the 2011 or 2012 populations and also in the 2014 population could not be assessed because the populations were selected from different versions of the research database.

The PHARMO subpopulations for which data records were available from the GP Database (for analysis of acne, other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management) represented 18% of the total study populations in 2011 and 2012 (1,415 new users in 2011 and 1,359 new users in 2012). In 2014 the overlap was larger: 321 of 1,401 (23%) users had GP information.

10.1.2 THIN participants

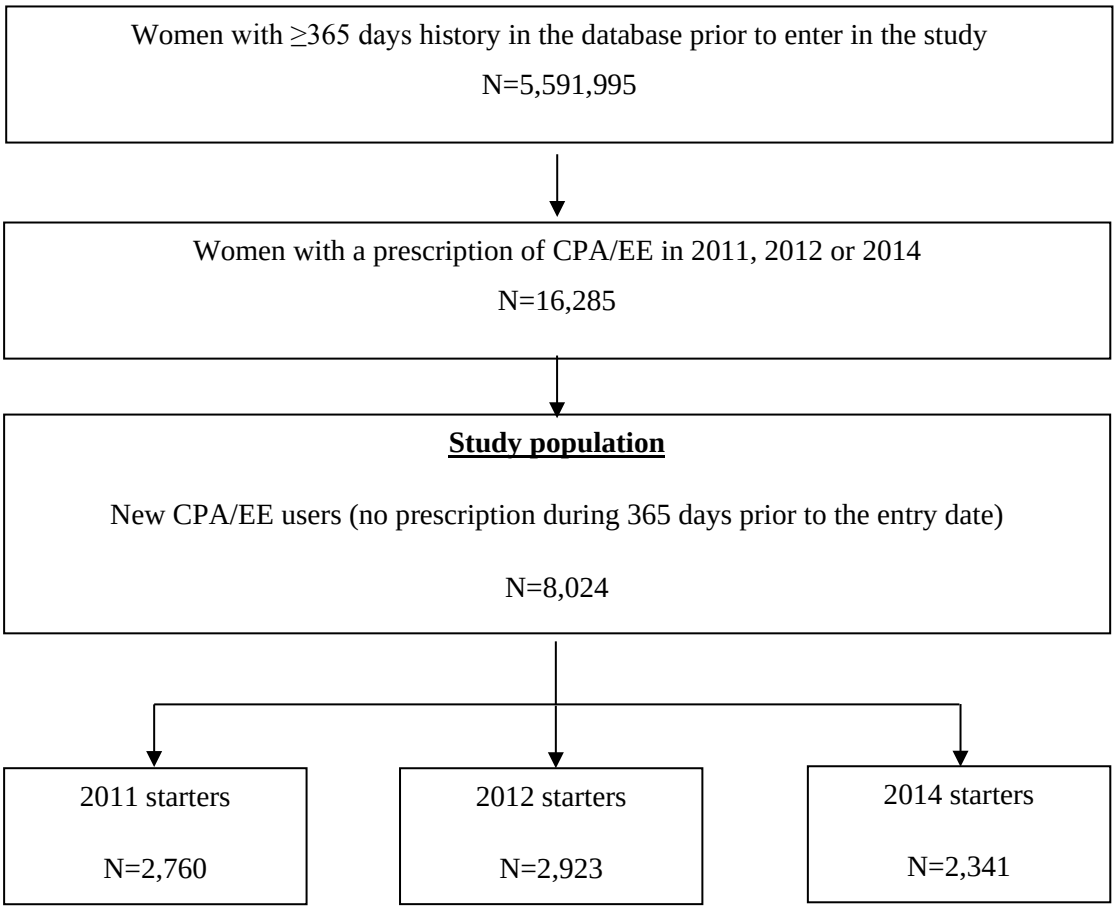

Figure 10.1.2.1 Flow chart of user selection in THIN

All women with a prescription of CPA/EE in 2011, 2012 or 2014 who were enrolled with the primary care physician for at least one year were selected from the THIN database (Figure 10.1.2.1). Women with a prescription of CPA/EE in 2011 or 2012 had to be free of CPA/EE for at least one year before entry date (start of the study year or database entry, whichever occurred first. See section 9.3). There were a total of 2,760 new users in 2011 and 2,923 new users in 2012. It should be noted that the two cohorts were mutually exclusive due to these eligibility criteria used in THIN. However, when changing the definition of being free of CPA/EE within the year prior to the index date instead of the entry date, there were a total of 108 additional users. Based on the small impact on the total number of users, we present the cohort of new users ascertained with the criteria of being free of CPA/EE within the year prior to start entering the study period (entry date). To ascertain new users during 2014, women had to be free of CPA/EE for at least one year before entry date (start of the study period or database entry, whichever occurred first). There were a total of 2,341 new users in 2014.

While the proportion of new users remained constant in 2011 and 2012, the proportion of new users slightly decreased in 2014. The proportions of new users were 1.6 per 1,000 women in 2011 (2,760/ 1,736,683), 1.6 per 1,000 women in 2012 (2,923/1,800,027) and 1.3 per 1,000 women in 2014 (2,341/1,869,071).

10.1.3 HSD participants

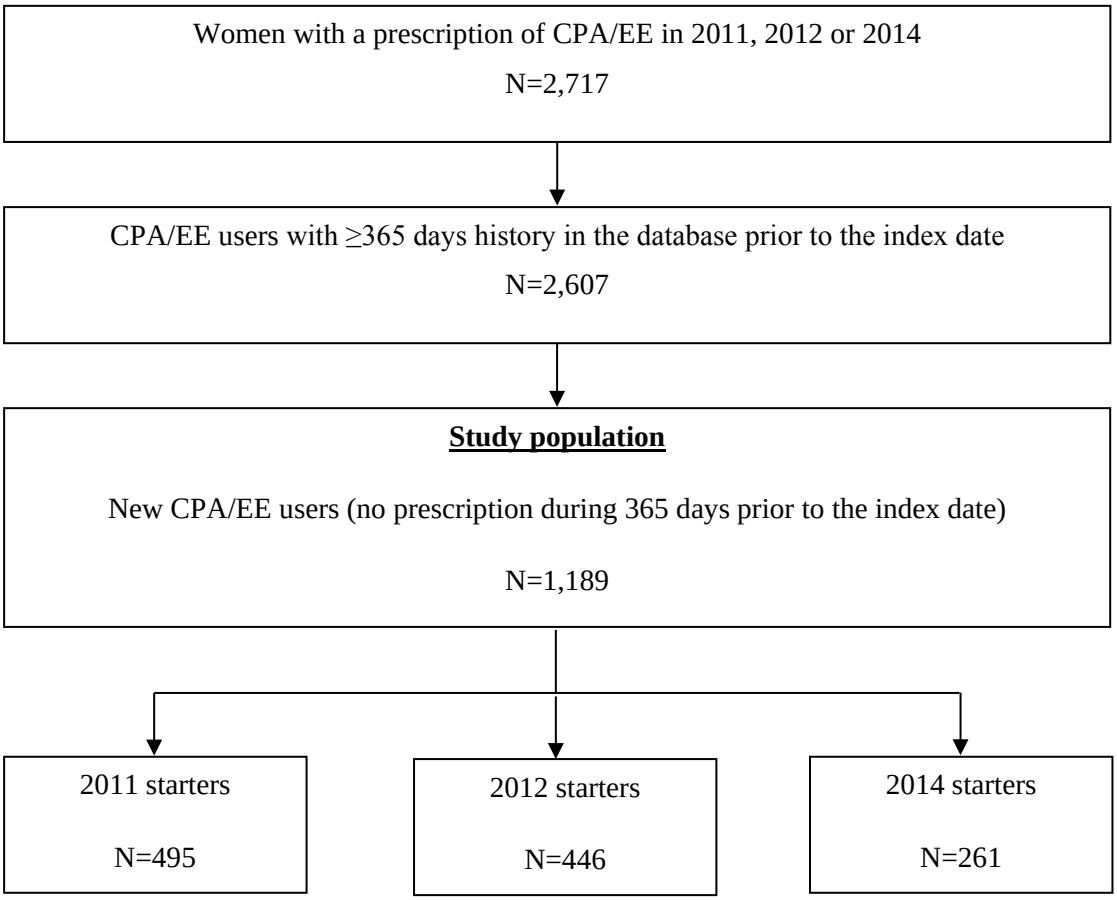

Figure 10.1.3.1 Flow chart of user selection in HSD

**Note: 13 users who were new users in 2011 as well as in 2012, i.e. stopped using CPA/EE in 2011 and re-started after more than 365 days in 2012, were included in both populations.*

All women with a prescription of CPA/EE in 2011, 2012 or 2014 were selected from the HSD GP records (Figure 10.1.3.1). The date of receiving the first prescription of CPA/EE in 2011, 2012 or 2014 was defined as the index date.

Women with less than 365 days history prior to the index date (N=110 (4%)) were excluded from the study population.

Many users, N=1,418 (54%), were prevalent user, i.e. had used CPA/EE during the year before the index date and were excluded from the final study population of new CPA/EE users. In total, 1,189 new users of CPA/EE were selected (some of whom were included in multiple study years, see below).

Three study populations were created for the study: 495 new users in 2011, 446 new users in 2012, 261 new users in 2014. Users who were new users in 2011 as well as in 2012, i.e. stopped using CPA/EE in 2011 and re-started after more than 365 days in 2012 (N=13), were included in both populations. The proportions of new users in the source population in the database were 0.8 per 1,000 women in 2011, 0.8 per 1,000 women in 2012 and 0.5 per 1,000 women in 2014.

10.2 Descriptive data

Table 10.2.1 General characteristics of new CPA/EE users in PHARMO, THIN and HSD in 2011, 2012 and 2014

	PHARMO			THIN			HSD		
	2011 starters N=7,876 n (%)	**2012 starters N=7,562 n (%)**	**2014 starters N=1,401 n (%)**	**2011 starters N=2,760 n (%)**	**2012 starters N=2,923 n (%)**	**2014 starters N=2,341 n (%)**	**2011 starters N=495 n (%)**	**2012 starters N=446 n (%)**	**2014 starters N=261 n (%)**
Age (years)									
<15	278 (4)	262 (3)	13 (1)	154 (6)	175 (6)	136 (6)	5 (1)	0 (0)	1 (<0.5)
15-<25	3,986 (51)	3,733 (49)	482 (34)	1,520 (55)	1,617 (55)	1,310 (56)	207 (42)	212 (48)	105 (40)
25-<35	2,385 (30)	2,365 (31)	584 (42)	866 (31)	907 (31)	709 (30)	146 (29)	120 (27)	83 (32)
35-<45	1,001 (13)	968 (13)	242 (17)	208 (8)	209 (7)	176 (8)	93 (19)	71 (16)	47 (18)
45-<55	211 (3)	229 (3)	73 (5)	11 (<0.5)	14 (<0.5)	10 (<0.5)	36 (7)	33 (7)	19 (7)
≥55	15 (<0.5)	5 (<0.5)	7 (<0.5)	1 (<0.5)	1 (<0.5)	0 (0)	8 (2)	10 (2)	6 (2)
mean ± SD	25 ± 9	25 ± 9	29 ± 9	23 ± 7	23 ± 7	23 ± 7	29 ± 10	29 ± 10	29 ± 11
median (IQR)	23 (18-31)	24 (18-31)	27 (23-34)	22 (17-28)	22 (17-28)	22 (17-28)	26 (21-36)	25 (21-35)	26 (21-36)
Database history before index date (years)									
1-<2	420 (5)	418 (6)	91 (6)	171 (6)	219 (7)	163 (7)	18 (4)	14 (3)	11 (4)
2-4	966 (12)	648 (9)	140 (10)	248 (9)	223 (8)	179 (8)	41 (8)	36 (8)	27 (10)
>4	6,490(82)	6,496 (86)	1,170 (84)	2,341 (84)	2,481 (85)	1,999 (85)	436 (88)	396 (89)	223 (85)
mean ± SD	8 ± 4	9 ± 4	9 ± 5	11 ± 6	12 ± 6	12 ± 7	11 ± 7	11 ± 6	12 ± 7
median (IQR)	7 (5-12)	8 (6-13)	9 (6-11)	12 (6-16)	12 (6-16)	13 (7-17)	11 (6-15)	11 (7-15)	12 (7-16)
Follow-up after index date									

	PHARMO			THIN			HSD		
	2011 starters N=7,876 n (%)	**2012 starters N=7,562 n (%)**	**2014 starters N=1,401 n (%)**	**2011 starters N=2,760 n (%)**	**2012 starters N=2,923 n (%)**	**2014 starters N=2,341 n (%)**	**2011 starters N=495 n (%)**	**2012 starters N=446 n (%)**	**2014 starters N=261 n (%)**
(months)*									
<6	3,877 (49)	3,573 (47)	641 (46)	1,316 (48)	1,351 (46)	1,108 (47)	232 (47)	224 (50)	118 (45)
6-12	3,999 (51)	3,989 (53)	760 (54)	1,444 (52)	1,572 (54)	1,233 (53)	263 (53)	222 (50)	143 (55)
mean ± SD	6 ± 3	6 ± 3	6 ± 3	6 ± 4	6 ± 4	6 ± 4	6 ± 4	6 ± 4	6 ± 4
median (IQR)	6 (3-9)	6 (3-9)	6 (3-9)	6 (3-9)	6 (3-9)	6 (3-9)	6 (3-9)	6 (3-9)	7 (3-10)

* by definition, the follow-up was not longer than 12 months (see section 9.3).

10.2.1 Descriptive data in PHARMO

Table 10.2.1 presents the general characteristics of new CPA/EE users in PHARMO. The mean age of new CPA/EE users in PHARMO was 25 ± 9 years in 2011 and 2012 and 29 ± 9 in 2014. Most users were between 15 and 25 years in 2011 (51%) and 2012 (49%); in 2014 the age group 25-35 was the largest (42%). The vast majority of CPA/EE initiators had more than 4 years of database history before the index date (82%-86%). Median length of follow up was 6 months (IQR 3-9) in all study years as defined by the 1-year study period.

10.2.2 Descriptive data in THIN

Table 10.2.1 presents the general characteristics of new CPA/EE users in THIN. The mean age of women was 23 ± 7 years in all study years. Most users were between 15 and 25 years (55% in 2011 and 2012 and 56% in 2014). The vast majority of CPA/EE initiators had more than 4 years of prospective recording history in the database before the index date (84% in 2011 and 85% in 2012 and 2014, respectively). Median length of follow up was 6 months (IQR 3-9) in all study years as defined by the 1-year study period.

10.2.3 Descriptive data in HSD

Table 10.2.1 presents the general characteristics of new CPA/EE users in HSD. The mean age of new CPA/EE users in HSD was 29 ± 10 years in 2011 and 2012 and was featured by a little higher variability in 2014 (29 ± 11 years). Most users were between 15 and 25 years (42% in 2011, 48% in 2012 and 40% in 2014). CPA/EE users aged between 25-35 years increased up to 32% in 2014 when compared with 2011 (29%) and 2012 (27%). The vast majority of CPA/EE initiators had more than 4 years of database history before the index date (88% in 2011, 89% in 2012 and 85% in 2014). Median length of follow up was 6 months (IQR 3-9) for 2011 and 2012, and 7 months (IQR 3-10) for 2014, as defined by the 1-year study period.

10.3 Outcome data

10.3.1 Treatment characteristics

Table 10.3.1.1 Treatment characteristics of new CPA/EE users in PHARMO, THIN and HSD in 2011, 2012 and 2014

	PHARMO			THIN			HSD		
	2011 starters N=7,876 n (%)	**2012 starters N=7,562 n (%)**	**2014 starters N=1,401 n (%)**	**2011 starters N=2,760 n (%)**	**2012 starters N=2,923 n (%)**	**2014 starters N=2,341 n (%)**	**2011 starters N=495 n (%)**	**2012 starters N=446 n (%)**	**2014 starters N=261 n (%)**
Type of CPA/EE									
Diane®-35	433 (5)	395 (5)	101 (7)	n.a.	n.a.	n.a.	405 (82)	369 (83)	215 (82)
Generic	7,443 (95)	7,164 (95)	1,300 (93)	n.a.	n.a.	n.a.	90 (18)	77 (17)	46 (18)
Unknown	0 (0)	3 (<0.5)	0 (0)	n.a.	n.a.	n.a.	0 (0)	0 (0)	0 (0)
CPA/EE prescriber									
GP	7,275 (92)	6,982 (92)	1,323 (94)	2,760 (100)	2,923 (100)	2,923 (100)	495 (100)	446 (100)	261 (100)
Dermatologist	208 (3)	195 (3)	21 (1)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Gynaecologist	177 (2)	165 (2)	27 (2)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Other specialist	216 (3)	217 (3)	30 (2)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Unknown	0 (0)	3 (<0.5)	0 (0)	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Number of CPA/EE episodes during follow-up									
1	5,996 (76)	5,668 (75)	1,095 (78)	2,277 (83)	2,374 (81)	1,830 (78)	328 (66)	280 (63)	176 (67)
2	1,542 (20)	1,540 (20)	244 (17)	422 (15)	465 (16)	439 (19)	110 (22)	115 (26)	59 (23)
3	301 (4)	308 (4)	57 (4)	56 (2)	78 (3)	69 (3)	40 (8)	35 (8)	19 (7)
4	37 (<0.5)	46 (1)	4 (<0.5)	5 (<0.5)	6 (<0.5)	3 (<0.5)	12 (2)	11 (2)	6 (2)
≥5	0 (0)	0 (0)	1 (<0.5)	0 (0)	0 (0)	0 (0)	4 (1)	5 (1)	1 (<0.5)
mean ± SD	1 ± 1	1 ± 1	1 ± 1	1 ± 0.5	1 ± 1	1± 1	1 ± 1	2 ± 1	1 ± 1

	PHARMO			THIN			HSD		
	2011 starters	**2012 starters**	**2014 starters**	**2011 starters**	**2012 starters**	**2014 starters**	**2011 starters**	**2012 starters**	**2014 starters**
	N=7,876	**N=7,562**	**N=1,401**	**N=2,760**	**N=2,923**	**N=2,341**	**N=495**	**N=446**	**N=261**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
median (IQR)	1 (1-1)	1 (1-2)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-1)	1 (1-2)	1 (1-2)	1 (1-2)
Summed duration of CPA/EE use (months) [1)]									
0-3	3,844 (49)	3,634 (48)	691 (49)	1,652 (60)	1,689 (58)	1,160 (50)	275 (56)	258 (58)	154 (59)
4-6	1,909 (24)	1,889 (25)	358 (26)	676 (25)	747 (26)	608 (26)	122 (25)	101 (23)	68 (26)
7-12	2,123 (27)	2,038 (27)	352 (25)	432 (16)	487 (17)	573 (24)	97 (20)	87 (20)	39 (15)
mean ± SD	5 ± 3	5 ± 3	4 ± 3	4 ± 3	4 ± 3	5 ± 3	4 ± 3	4 ± 3	3 ± 3
median (IQR)	4 (3-7)	4 (3-7)	4 (3-7)	3 (3-6)	3 (3-6)	4 (3-7)	3 (2-6)	3 (2-6)	2 (1-5)
Concomitant use of CPA/EE and other HC									
Concomitant	211 (3)	122 (2)	30 (2)	15 (1)	11 (<0.5)	8 (<0.5)	4 (1)	3 (1)	4 (2)
Concomitant and potential concomitant [2)]	15 (<0.5)	12 (<0.5)	5 (<0.5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Potential concomitant	2,000 (25)	1,928 (25)	350 (25)	110 (4)	142 (5)	96 (4)	20 (4)	9 (2)	4 (2)
Non-concomitant	688 (9)	815 (11)	160 (11)	129 (5)	125 (4)	91 (4)	38 (8)	35 (8)	23 (9)
No use of other HC	4,962 (63)	4,685 (62)	856 (61)	2,506 (91)	2,645 (90)	2,146 (92)	433 (87)	399 (89)	230 (88)
Duration of concomitant use of CPA/EE and other HC	N=226	N=134	N=35	N=15	N=11	N=8	N=4	N=3	N=4
≤28 days concomitant use	21 (9)	8 (6)	1 (3)	3 (20)	1 (9)	1 (12)	[3)]	[3)]	[3)]
>28 - 84 days concomitant use	145 (64)	101 (75)	31 (89)	6 (40)	6 (55)	4 (50)	[3)]	[3)]	[3)]
>84 days concomitant	60 (27)	25 (19)	3 (9)	6 (40)	4 (36)	3 (37)	[3)]	[3)]	[3)]

	PHARMO			THIN			HSD		
	2011 starters	**2012 starters**	**2014 starters**	**2011 starters**	**2012 starters**	**2014 starters**	**2011 starters**	**2012 starters**	**2014 starters**
	N=7,876	**N=7,562**	**N=1,401**	**N=2,760**	**N=2,923**	**N=2,341**	**N=495**	**N=446**	**N=261**
	n (%)	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
use									
mean ± SD	89 ± 53	90 ± 46	85 ± 44	92 ± 67	91 ± 53	87 ± 37	3)	3)	3)
median (IQR)	78 (73-88)	78 (78-78)	78 (78-78)	84 (47-90)	84 (56-90)	77 (67-114)	3)	3)	3)
Duration of potential concomitant use of CPA/EE and other HC (days)	N=2,015	N=1,940	N=355	N=110	N=142	N=96	N=20	N=9	N=4
≤28 days potential concomitant use	518 (26)	532 (27)	102 (29)	41 (37)	62 (44)	46 (48)	8 (40)	6 (67)	3)
>28 - 84 days potential concomitant use	892 (44)	812 (42)	160 (45)	56 (51)	63 (44)	40 (42)	10 (50)	2 (22)	3)
>84 days potential concomitant use	605 (30)	596 (31)	93 (26)	13 (12)	17 (12)	10 (10)	2 (10)	1 (11)	3)
mean ± SD	82 ± 62	85 ± 63	80 ± 59	52 ± 32	53 ± 35	47 ±34	42 ± 28	35 ± 19	3)
median (IQR)	63 (28-112)	63 (28-112)	56 (28-106)	50 (28-68)	50 (28-76)	34 (28-58)	29 (28-56)	28 (28-29)	3)

1) by definition, the follow-up and thus summed duration of use was not longer than 12 months (see section 9.3). 2) A user could be concomitant and potential concomitant user at different times during CPA/EE use. This was observed in PHARMO only. 3) Summary statistics from <5 individuals are not reported.

Table 10.3.1.2 Concomitant use of CPA/EE and other HC in PHARMO and THIN in 2011, 2012 and 2014

	PHARMO			THIN		
	2011 starters n (%)	**2012 starters n (%)**	**2014 starters n (%)**	**2011 starters n (%)**	**2012 starters n (%)**	**2014 starters n (%)**
Concomitant use with 28 days cycle HC	**N=1,920**	**N=1,780**	**N=321**	**N=111**	**N=140**	**N=70**
Concomitant	192 (10)	118 (7)	30 (9)	13 (13)	9 (6)	4 (6)
Concomitant and potential concomitant	12 (<1)	12 (<1)	3 (1)	0 (0)	0 (0)	0 (0)
Potential concomitant	1,716 (89)	1,650 (93)	288 (90)	98 (87)	131 (94)	66 (94)
Duration of concomitant use	N=204	N=130	N=33	N=13	N=9	N=4
≤28 days	19 (9)	7 (5)	1 (3)	3 (23)	1 (11)	1)
>28 - 84 days	132 (65)	99 (76)	29 (88)	6 (46)	5 (56)	1)
>84 days	53 (26)	24 (18)	3 (9)	4 (31)	3 (33)	1)
mean ± SD	89 ± 52	90 ± 47	85 ± 45	92 ± 73	94 ± 58	1)
median (IQR)	78 (76-86)	78 (78-78)	78 (78-78)	84 (47-86)	84 (56-89)	1)
Duration of potential concomitant use	N=1,728	N=1,662	N=291	N=98	N=131	N=66
≤28 days	478 (28)	499 (30)	91 (31)	40 (41)	60 (46)	36 (55)
>28 - 84 days	788 (46)	700 (42)	137 (47)	48 (49)	56 (43)	24 (36)
>84 days	462 (27)	463 (28)	63 (22)	10 (10)	15 (11)	6 (9)
mean ± SD	75 ± 55	79 ± 55	73 ± 51	50 ± 32	52 ± 35	44 ± 30
median (IQR)	56 (28-97)	56 (28-106)	56 (28-84)	46 (28-66)	46 (28-74)	28 (28-56)
Concomitant use with LARC HC	**N=324**	**N=313**	**N=67**	**N=14**	**N=13**	**N=34**
Concomitant	20 (6)	4 (1)	0 (0)	2 (14)	2 (18)	4 (12)
Concomitant and potential concomitant	7 (2)	5 (2)	3 (4)	0 (0)	0 (0)	0 (0)
Potential concomitant	297 (92)	304 (97)	64 (96)	12 (86)	11 (82)	30 (88)
Duration of concomitant use	N=27	N=9	N=3	N=2	N=2	N=4
≤28 days	2 (7)	1 (11)	1)	1)	1)	1)

	PHARMO			THIN		
	2011 starters n (%)	**2012 starters n (%)**	**2014 starters n (%)**	**2011 starters n (%)**	**2012 starters n (%)**	**2014 starters n (%)**
>28 - 84 days	15 (56)	6 (67)	1)	1)	1)	1)
>84 days	10 (37)	2 (22)	1)	1)	1)	1)
mean ± SD	93 ± 62	80 ± 35	1)	1)	1)	1)
median (IQR)	78 (53-122)	84 (78-84)	1)	1)	1)	1)
Duration of potential concomitant use	N=304	N=309	N=67	N=12	N=11	N=30
≤28 days	43 (14)	35 (11)	11 (16)	1 (8)	2 (18)	10 (33)
>28 - 84 days	110 (36)	127 (41)	25 (37)	8 (67)	7 (64)	16 (53)
>84 days	151 (50)	147 (48)	31 (46)	3 (25)	2 (18)	4 (13)
mean ± SD	121 ± 85	122 ± 87	114 ± 79	67 ± 33	72 ± 32	52 ± 40
median (IQR)	84 (62-165)	81 (57-162)	79 (57-156)	62 (38-89)	75 (43-84)	44 (27-66)
Non-concomitant	**688**	**815**	**160**	**129**	**125**	**91**
No use of other HC	**4,962**	**4,685**	**856**	**2,506**	**2,645**	**2,146**

Note that the groups of 28 days cycle HC and LARC users may add up to more that the sum of (potential) concomitant users in Table 10.3.1.1, as a user may be in both groups. HSD did not capture LARC. 1) Summary statistics from <5 individuals are not reported.

10.3.1.1 Treatment characteristics in PHARMO

Table 10.3.1.1 presents the CPA/EE treatment characteristics of new users in PHARMO in 2011, 2012 and 2014. The type of CPA/EE was determined at the index prescription. Generic CPA/EE was most often prescribed; in 2011 and 2012 95% used generic CPA/EE and 5% used Diane®-35 and in 2014 93% used generic CPA/EE and 7% used Diane®-35. Most prescriptions were issued by GPs (92% in 2011 and 2012 and 94% in 2014). Other specified prescribers were dermatologists (1-3%) or gynaecologists (2%). Most users (75-78%) had one episode of uninterrupted CPA/EE use during follow-up. More than two CPA/EE episodes within one year were observed for 4-5% of users.

The median summed duration of CPA/EE use, i.e. during all treatment episodes during follow-up, was 4 months (IQR 3-7) in all study years. Note that this duration was limited by the available follow-up (see section 9.3). The median duration of individual CPA/EE prescriptions was 84 days (IQR 84-84) (data not shown).

Concomitant use of CPA/EE and other HC (28 days cycle HC or LARC) was observed for 3% of CPA/EE users in 2011 and for 2% of CPA/EE users in 2012 and 2014. These users had completely overlapping treatment episodes of CPA/EE and other HC. In addition, potential concomitant use of CPA/EE with other HC was observed for 26% of CPA/EE users in 2011 and 2012 and 25% in 2014 (note the small group of concomitant as well as potential concomitant use episodes observed). These users were starting CPA/EE or other HC before the end date of the other drug dispensing. As the exposure was based on prescriptions, the users were likely to discontinue the previous drug. The median duration of individual 28 days cycle HC prescriptions was 168 days (IQR 84-168) in 2011 and 2012 and 84 days (IQR 84-168) in 2014; the median duration of LARC HC prescriptions was 90 days (IQR 84-1825) in 2011 and 2012 and 1825 days (IQR 84-1825) in 2014 (data not shown). Among CPA/EE users in all study years, 61-63% did not have any other HC prescription during the study period.

The estimated duration of concomitant as well as potential concomitant use was mostly between 28 and 84 days. Median durations were 78 days for concomitant use in all study years and 63 days for potential concomitant use in 2011 and 2012 and 56 days for potential concomitant use in 2014.

Table 10.3.1.2 presents the concomitant use of CPA/EE and other HC by type of HC (28 days cycle HC and LARC) in PHARMO. Note that the groups of 28 days cycle HC and LARC users may add up to more than the sum of (potential) concomitant users in Table 10.3.1.1, as a user may be in both groups. As 28 days cycle HC was more frequently used than LARC (for example, 89% of HC users in 2011 used 28 days cycle (33% of study population)), this was also the most frequent type used concomitantly with CPA/EE.

The median duration of concomitant use was similar among 28 days cycle HC users (78 days in all study years) and LARC users (78 days in 2011 and 84 days in 2012; too few users in

2014). The median duration of potential concomitant use was longer among LARC users: 79-84 days for LARC and 56 days for 28 days cycle HC. Note that the longer durations of potential concomitant use were probably by definition as duration of LARC use is longer. In addition, removal dates of intra-uterine devices and implants are not always captured in the database.

10.3.1.2 Treatment characteristics in THIN

Table 10.3.1.1 presents the CPA/EE treatment characteristics of new users in THIN in 2011 and 2012 and 2014. Most users (81-83%) had only one uninterrupted episode of CPA/EE during 2011 and 2012 and a similar proportion (78%) was found in 2014. More than two CPA/EE episodes within one year were observed for 2-3% of users

The median summed duration of CPA/EE use, i.e. during all treatment episodes during follow-up, was 3 months (IQR 3-6) in 2011 and 2012 and 4 months (IQR 3-7) in 2014. Note that this duration was limited by the available follow-up (see section 9.3). The median duration of individual CPA/EE prescriptions was 96 days (IQR 84-168) for 2011 and 2012 and 117 days (IQR 84-197) for 2014 (data not shown).

Concomitant use of CPA/EE and other HC (28 days cycle HC or LARC) was rare with 1% of CPA/EE users in 2011 and < 0.5% of CPA/EE users in 2012 and 2014 (Table 11.3.1.1). These users had completely overlapping treatment episodes of CPA/EE and other HC. In addition, potential concomitant use of CPA/EE and other HC was observed for 4% of CPA/EE users in 2011, 5% in 2012 and 4% in 2014. The median duration of individual 28 days cycle HC prescriptions was 63 days (IQR 63-126) in 2011 and 2012 and 84 days (IQR 84-84) in 2014 and the median duration of LARC HC prescriptions was 1,095 days (IQR 90-1,095) in 2011 and 2012 and 1,095 days (IQR 90-1,095) in 2014 (data not shown). Among CPA/EE users in 2011, 2012 and 2014, respectively, 91%, 90% and 92% did not have any other HC prescription during the study period (data not shown).

The estimated median duration of concomitant use was 84 days (IQR 47-90 in 2011 and 56-90 in 2012) and 77 days (IQR 67-114) in 2014. For potential concomitant use this was 50 days (IQR 28-68 in 2011 and 28-76 in 2012) and 34 days (IQR 28-58) in 2014 (Table 10.3.1.1).

Table 10.3.1.2 presents the concomitant use of CPA/EE and other HC by type of HC (28 days cycle HC and LARC) in THIN. As 28 days cycle HC was more frequently used than LARC (for example, 87% of HC users in 2011 used 28 days cycle, 92% in 2012 and 67% in 2014), this was also the most frequent type used concomitantly with CPA/EE.

The median duration of concomitant use among 28 days cycle HC users was 84 days (IQR 47-86 in 2011 and 56-89 in 2012). The number of concomitant 28 days cycle users in 2014 as well as the number of concomitant LARC users in all study years was too low to report

summary statistics. The median duration of potential concomitant use of 28 days cycle HC was 46 days (IQR 28-66) in 2011, 46 days (IQR 28-74) in 2012 and 28 (28-56) days in 2014. A total of 41% of potential concomitant users of 28 days cycle HC had a potential concomitant period of less than 28 days in 2011, 46% in 2012 and 55% in 2014. For LARC, corresponding median durations were 62 days (IQR 38-89) in 2011, 75 days (IQR 43-84) in 2012 and 44 days (IQR 27-66) in 2014. These numbers should be interpreted with caution as numbers were low and actual removal dates were not consistently captured in the database.

10.3.1.3 Treatment characteristics in HSD

Table 10.3.1.1 presents the CPA/EE treatment characteristics of new users in HSD in 2011, 2012 and 2014. The type of CPA/EE was determined at the index prescription. In HSD, Diane®-35 use was more frequent than generics (82% in 2011, 83% in 2012 and 82% in 2014) and all prescriptions were from GP, as this was the data source for the prescriptions. Most users (66% in 2011, 63% in 2012 and 67% in 2014) had one episode of uninterrupted CPA/EE use during follow-up. More than two CPA/EE episodes within one year were observed for 7-8% (3 episodes), 2% (4 episodes), and 0.5-1% (5 or more episodes) of users, respectively.

The median summed duration of CPA/EE use, i.e. during all treatment episodes during follow-up, was 3 months (IQR 2-6) in 2011 and 2012 and 2 (1-5) in 2014. Note that this duration was limited by the available follow-up (see section 9.3). The median duration of individual prescriptions was 56 days for both CPA/EE (IQR 56-56) and other HC (IQR 28-56) (data not shown).

Concomitant use of CPA/EE and HC was observed for 1% of the users in HSD in 2011 and 2012 and for 2% of the users in 2014. These users had completely overlapping treatment episodes of CPA/EE and HC. In addition, potential concomitant use of CPA/EE and HC was observed for 4% in 2011 and 2% in 2012 and 2014. These users were starting CPA/EE or HC before the end date of the other drug prescription. As the exposure was based on prescriptions, the users were likely to discontinue the previous drug. Among CPA/EE users, 87% (2011), 89% (2012) and 88% (2014) did not have any HC prescription during the study period.

HSD had too few users with concomitant use (N=4 in 2011 and 2014 and 3 in 2012), or with potential concomitant use in 2014 (N=4) to report summary statistics concerning durations of concomitant use. For potential concomitant use, the median duration was 29 days (IQR 28-56) in 2011 and 28 days (IQR 28-29) in 2012.

10.3.2 Diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management

Table 10.3.2.1 Diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management 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=1,415 n (%)	**2012 starters N=1,359 n (%)**	**2014 starters N=321 n (%)**	**2011 starters N=2,760 n (%)**	**2012 starters N=2,923 n (%)**	**2014 starters N=2,341 n (%)**	**2011 starters N =495 n (%)**	**2012 starters N=446 n (%)**	**2014 starters N=261 n (%)**
Any hyperandrogenic condition	**284 (20)**	**268 (20)**	**52 (16)**	**1,671 (61)**	**1,812 (62)**	**1,468 (63)**	**108 (22)**	**109 (24)**	**63 (24)**
Acne	241 (17)	219 (16)	38 (12)	1,414 (51)	1,570 (54)	1,281 (55)	68 (14)	76 (17)	37 (14)
Alopecia	17 (1)	22 (2)	7 (2)	41 (2)	35 (1)	31 (1)	9 (2)	7 (2)	6 (2)
Seborrhoea	11 (1)	9 (1)	0 (0)	0 (0)	1 (<0.5)	0 (0)	0 (0)	0 (0)	0 (0)
Hirsutism	17 (1)	21 (2)	5 (2)	110 (4)	90 (3)	78 (3)	19 (4)	13 (3)	7 (3)
PCOS	5 (<0.5)	1 (<0.5)	2 (1)	185 (7)	196 (7)	149 (6)	17 (3)	19 (4)	16 (6)
Menstrual problems**	**40 (3)**	**41 (3)**	**11 (3)**	**147 (5)**	**147 (5)**	**81 (4)**	**27 (5)**	**21 (5)**	**16 (6)**
Menstrual disorder	37 (3)	37 (3)	6 (2)	121 (4)	122 (4)	66 (3)	14 (3)	7 (2)	5 (2)
Oligomenorrhoea/amenorrhoea	3 (<0.5)	4 (<0.5)	5 (2)	30 (1)	31 (1)	18 (1)	13 (3)	16 (4)	11 (4)
Contraceptive management***	**183 (13)**	**198 (15)**	**39 (12)**	**620 (22)**	**682 (23)**	**461 (20)**	**55 (11)**	**41 (9)**	**18 (7)**

* For the assessment of recent hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management, the subpopulation of users with GP data available was used in PHARMO. Note that the groups within hyperandrogenic conditions may overlap as individuals may have more than one diagnosis.
** In the absence of any of the hyperandrogenic conditions above. Note that the groups with menstrual disorder and oligomenorrhoea/amenorrhoea may overlap.
*** In the absence of any of the hyperandrogenic conditions or menstrual problems above.

10.3.2.1 Diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management in PHARMO

Table 10.3.2.1 presents the proportions of new CPA/EE users with diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management in the year prior to index date in PHARMO. In 2011 and 2012, a recent (within 365 days) diagnosis of any of the hyperandrogenic conditions was identified for 20% of CPA/EE users: respectively 17% and 16% had a recent acne diagnosis and proportions with other diagnoses (alopecia, seborrhoea, hirsutism or PCOS) were each 2% or less. For 3% of the remaining CPA/EE users, i.e. without any hyperandrogenic diagnosis, menstrual problems were recorded in the year preceding the index date and another 13% in 2011 and 15% in 2012 visited the GP for contraceptive management.

In 2014 a recent diagnosis of any of the hyperandrogenic conditions was identified for 16% of CPA/EE users, with 12% diagnosed with acne. Among the remaining users without any hyperandrogenic diagnosis, 3% had recorded menstrual problems and another 12% visited the GP for contraceptive management.

10.3.2.2 Diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management in THIN

Table 10.3.2.1 presents the proportions of new CPA/EE users with diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management in the year prior to index date in THIN. In 2011 and 2012, a recent (within 365 days) diagnosis of any of the hyperandrogenic conditions was identified for 61% and 62% of CPA/EE users, respectively: 51% and 54% had a recent acne diagnosis and proportions with other diagnoses were 1-2% for alopecia, <0.5% for seborrhoea, 3-4% for hirsutism and 7% for PCOS. For 5% of the remaining CPA/EE users, i.e. without any hyperandrogenic diagnosis, menstrual problems were recorded in the year preceding the index date and another 22% in 2011 and 23% in 2012 had an entry for contraceptive management.

In 2014, diagnosis of any of the hyperandrogenic conditions was present among 63% of CPA/EE users: 55% had a recent acne diagnosis and proportions with other diagnoses were 1% for alopecia, 3% for hirsutism and 6% for PCOS. For 4% of the remaining CPA/EE users, i.e. without any hyperandrogenic diagnosis, menstrual problems were recorded in the year preceding the index date and another 20% had an entry for contraceptive management.

10.3.2.3 Diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management in HSD

Table 10.3.2.1 presents the proportions of new CPA/EE users with diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive

management in the year prior to index date in HSD. In 2011 and 2012, a recent (within 365 days) diagnosis of any of the hyperandrogenic conditions was identified for 22% and 24% of CPA/EE users, respectively: 14% and 17% had a recent acne diagnosis and proportions with other diagnoses (alopecia, seborrhoea, hirsutism or PCOS) were each 4% or less. For the remaining CPA/EE users without any hyperandrogenic diagnosis, 5% reported menstrual problems in the year preceding the index date and another 11% in 2011 and 9% in 2012 contacted the GP for contraceptive management.

In 2014, diagnosis of any of the hyperandrogenic conditions was present among 24% of CPA/EE users: 14% had a recent acne diagnosis and proportions with other diagnoses were 2% for alopecia, 3% for hirsutism and 6% for PCOS. For 6% of the remaining CPA/EE users, i.e. without any hyperandrogenic diagnosis, menstrual problems were recorded in the year preceding the index date and another 7% were encoded for contraceptive management.

10.3.3 Acne diagnosis and treatment

Table 10.3.3.1 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=1,415	**2012 starters N=1,359**	**2014 starters N=321**	**2011 starters N=2,760**	**2012 starters N=2,923**	**2014 starters N=2,341**	**2011 starters N=495**	**2012 starters N=446**	**2014 starters N=261**
Users with acne diagnosis	**N=241 n (%)**	**N=219 n (%)**	**N=38 n (%)**	**N=1,414 N (%)**	**N=1,570 N (%)**	**N=1,281 N (%)**	**N=68 n (%)**	**N=76 n (%)**	**N=37 n (%)**
Any acne treatment	146 (61)	138 (63)	21 (55)	1,174 (83)	1,300 (83)	1,072 (84)	13 (19)	20 (26)	7 (19)
Topicals									
Topical antibiotics	69 (29)	62 (28)	9 (24)	581 (41)	675 (43)	544 (42)	4 (6)	6 (8)	3 (8)
Corticosteroids in topical combinations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Topical retinoids	32 (13)	30 (14)	4 (11)	241 (17)	319 (20)	295 (23)	4 (6)	1 (1)	0 (0)
Other topical preparations	20 (8)	20 (9)	3 (8)	192 (14)	251 (16)	133 (10)	0 (0)	0 (0)	1 (3)
Systemic preparations									
Systemic retinoids	0 (0)	0 (0)	0 (0)	4 (<0.5)	0 (0)	0 (0)	3 (4)	5 (7)	0 (0)
Systemic antibiotics	42 (17)	35 (16)	1 (3)	541 (38)	695 (44)	601 (47)	3 (4)	10 (13)	4 (11)
Hormonal agents									
Hormonal contraceptives	68 (28)	67 (31)	14 (37)	547 (39)	511 (33)	454 (35)	0 (0-	0 (0	0 (0)
Antiandrogens	0 (0)	3 (1)	0 (0)	1 (<0.5)	1 (<0.5)	0 (0)	1 (1)	0 (0	0 (0)
Users without acne diagnosis	**N=1,174 n (%)**	**N=1,140 n (%)**	**N=283 n (%)**	**N=1,346 n (%)**	**N=1,353 n (%)**	**N=1,060 n (%)**	**N=427 n (%)**	**N=370 n (%)**	**N=224 n (%)**
Any acne treatment	531 (45)	484(42)	112 (40)	677 (50)	726 (54)	553 (52)	27 (6)	17 (5)	11 (5)
Topicals									
Topical antibiotics	123 (10)	130 (11)	17 (6)	126 (9)	161 (12)	139 (13)	5 (1)	1 (<0.5)	3 (1)

	PHARMO*			THIN			HSD		
	2011 starters N=1,415	**2012 starters N=1,359**	**2014 starters N=321**	**2011 starters N=2,760**	**2012 starters N=2,923**	**2014 starters N=2,341**	**2011 starters N=495**	**2012 starters N=446**	**2014 starters N=261**
Corticosteroids in topical combinations	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Topical retinoids	59 (5)	58 (5)	4 (1)	41 (3)	41 (3)	48 (5)	1 (<0.5)	0 (0)	2 (1)
Other topical preparations	19 (2)	26 (2)	3 (1)	38 (3)	40 (3)	36 (3)	0 (0)	0 (0)	1 (<0.5)
Systemic preparations									
Systemic retinoids	0 (0)	0 (0)	0 (0)	1 (<0.5)	1 (<0.5)	0 (0)	1 (<0.5)	4 (1)	0 (0)
Systemic antibiotics	109 (9)	106 (9)	12 (4)	134 (10)	149 (11)	133 (13)	19 (4)	10 (3)	7 (3)
Hormonal agents									
Hormonal contraceptives	372 (32)	337 (29)	93 (33)	518 (38)	548 (41)	388 (37)	0 (0)	0 (0)	0 (0)
Antiandrogens	3 (<0.5)	5 (<0.5)	0 (0)	7 (1)	3 (<0.5)	0 (0)	3 (1)	2 (1)	1 (<0.5)

* For the assessment of acne treatment, the subpopulation of users with GP data available was used in PHARMO.

10.3.3.1 Acne diagnosis and treatment in PHARMO

Table 10.3.3.1 presents the proportions of new CPA/EE users with acne treatment by recent acne diagnosis in the year prior to index date (as presented in Table 10.3.2.1) in PHARMO in 2011, 2012 and 2014.

In 2011 and 2012, among CPA/EE users with an acne diagnosis, 61% and 63% had a record of acne treatment during the previous year in PHARMO. Recent acne treatment was also observed among users without an acne diagnosis in the year prior to index date (42-45%). Overall, the percentage of CPA/EE users with recent acne diagnosis and/or treatment was 55% in 2011 (772 (241 diagnosed and 531 treated but without diagnosis) of 1,415) and 52% in 2012 (703 (219 diagnosed and 484 treated but without diagnosis) of 1,359).

In 2014, among CPA/EE users with an acne diagnosis, 55% had a record of acne treatment during the previous year in PHARMO. Recent acne treatment was also observed for 40% of users without an acne diagnosis in the year prior to index date; overall, the percentage of CPA/EE users with recent acne diagnosis and/or treatment in 2014 was 47%: 150 (38 diagnosed and 112 treated but without diagnosis) of 321.

Note that a major proportion of “acne treatment” was HC: 28-37% of women with an acne diagnosis and 29-33% of women without an acne diagnosis had used HC in the year before starting CPA/EE. Apart from HC, topical antibiotics were the most widely used acne treatment among women with acne diagnosis (24-29%) as well as among women without acne diagnosis (6-11%) during the study periods. While in 2011 and 2012 17% and 16% of women with an acne diagnosis had used systemic antibiotics, only 3% had recently used systemic antibiotics in 2014.

10.3.3.2 Acne diagnosis and treatment in THIN

Table 10.3.3.1 presents the proportions of new CPA/EE users with acne treatment by recent acne diagnosis in the year prior to index date (as presented in Table 10.3.2.1) in THIN in 2011, 2012 and 2014.

In 2011 and 2012, among CPA/EE users with an acne diagnosis, 83% had a record of acne treatment during the previous year in THIN. Recent acne treatment was also observed among users without an acne diagnosis in the year prior to index date (50-54%). Overall, the percentage of CPA/EE users with recent acne diagnosis and/or treatment was 76% in 2011 (2,091 (1,414 diagnosed and 677 treated but without diagnosis) of 2,760) and 79% in 2012 (2,296 (1,570 diagnosed and 726 treated but without diagnosis) of 2,923).

In 2014, among CPA/EE users with an acne diagnosis, 84% had a record of acne treatment during the previous year in THIN. Recent acne treatment was also observed for 52% of users without an acne diagnosis in the year prior to index date; overall, the percentage of CPA/EE

users with recent acne diagnosis and/or treatment in 2014 was 78%: 1,834 (1,281 diagnosed and 553 treated but without diagnosis) of 2,341.

Note that a major proportion of “acne treatment” was HC: 33-39% of women with an acne diagnosis and 37-41% of women without an acne diagnosis had used HC in the year before starting CPA/EE. Apart from HC, topical or systemic antibiotics were the most frequently observed of the selected treatments among women with acne diagnosis (41-43% received topical antibiotics and 38-47% received systemic antibiotics) as well as among women without acne diagnosis (9-13% and 10-13%, respectively) during the study periods.

10.3.3.3 Acne diagnosis and treatment in HSD

Table 10.3.3.1 presents the proportions of new CPA/EE users with acne treatment by recent acne diagnosis in the year prior to index date (as presented in Table 10.3.2.1) in HSD in 2011, 2012 and 2014.

In 2011 and 2012, among CPA/EE users with an acne diagnosis, 19% and 26% had a record of acne treatment during the previous year in HSD. Recent acne treatment was also observed among users without an acne diagnosis in the year prior to index date (5-6%). Overall, the percentage of CPA/EE users with recent acne diagnosis and/or treatment was 19% in 2011 (95 (68 diagnosed and 27 treated but without diagnosis) of 495) and 21% in 2012 (93 (76 diagnosed and 17 treated but without diagnosis) of 446).

In 2014, among CPA/EE users with an acne diagnosis, 19% had a record of acne treatment during the previous year in HSD. Recent acne treatment was also observed for 5% of users without an acne diagnosis in the year prior to index date; overall, the percentage of CPA/EE users with recent acne diagnosis and/or treatment was 18%: 48 (37 diagnosed and 11 treated but without diagnosis) of 261.

Topical or systemic antibiotics were the most frequently observed of the selected treatments among women with acne diagnosis (6-8% received topical antibiotics and 4-13% received systemic antibiotics) in 2011, 2012 and 2014. Among women without acne diagnosis, mainly systemic antibiotic prescriptions were observed (3-4%) during the study periods.

10.4 Main results

10.4.1 Main results in PHARMO

The PHARMO study population for the interim analysis included 7,876 new CPA/EE users in 2011 and 7,562 new CPA/EE users in 2012. In 2014, for the final analysis, 1,401 new users were included. The proportions of new users in each year were 2.8 per 1,000 women in 2011, 2.6 per 1,000 women in 2012 and 0.7 per 1,000 women in 2014.

About 50% of users were between 15 and 25 years old in 2011 and 2012 (mean age at initiation 25 years); in 2014 new users were slightly older (mean age 29 years). One year history was required for assessment of acne or other hyperandrogenic conditions; the median available history in the database was 7-9 years. Follow-up after the index date was restricted by the end of the study period (calendar year of index date) and therefore the median follow-up was 6 months. During this follow-up period, the majority of women (75-78%) had one uninterrupted episode of CPA/EE.

Most prescriptions (93-95%) were generic CPA/EE. CPA/EE users were selected from the out-patient pharmacy dispensing records, which includes also specialist prescriptions. Most of the prescriptions (92-94%) were issued by GPs; dermatologists, gynaecologists and other specialists accounted for 6-8%. The median estimated duration of use per calendar year cohort was 4 months.

The conditions considered treatment indications for CPA/EE were assessed among a subpopulation with GP records available (1,415 in 2011, 1,359 in 2012 and 321 in 2014). Prevalences were: acne (17% in 2011, 16% in 2012, and 12% in 2014), alopecia and hirsutism (both 1-2% over the study periods), seborrhoea and PCOS (both up to 1%). Individuals may have had more than one of these conditions. Of the remaining CPA/EE users, i.e. without any hyperandrogenic diagnosis, 3% had menstrual problems and another 12-15% (13% in 2011, 15% in 2012 and 12% in 2014) recently visited the GP for contraceptive management.

Among women with an acne diagnosis recorded in the year prior to the index date, 61% in 2011, 63% in 2012 and 55% in 2014 had received acne treatment during that year. Among women without an acne diagnosis, 45% received acne treatment within the year prior to the index date in 2011, 42% in 2012 and 40% in 2014. The proportions of users with either acne diagnosis or treatment were thus 55% in 2011, 52% in 2012 and 47% in 2014.

Note that a major proportion of acne treatment was HC: 28-37% of women with an acne diagnosis and 29-33% of women without an acne diagnosis had used HC in the year before starting CPA/EE. Apart from HC, topical antibiotics were the most widely used acne treatment among women with acne diagnosis (24-29%) as well as among women without acne diagnosis (6-11%) during the study periods. While 17% of women with acne diagnosis had used systemic antibiotics in 2011 and 16% in 2012, only 3% had recently used systemic antibiotics in 2014.

Concomitant use of other HC was observed for 226 (3%) of new CPA/EE users in 2011 and for 2% of new CPA/EE users in 2012 and 2014 (134 and 35 users, respectively). The median duration of concomitant use was 78 days in all study years. These concomitant users had completely overlapping treatment episodes of CPA/EE and other HC.

Another 25% of new CPA/EE users in all study years were potential concomitant users who started CPA/EE or other HC before the end date of the other drug prescription. The median duration of this potential overlap was 63 days in 2011 and 2012 and 56 days in 2014. Most concomitant use was observed with 28 days cycle HC.

For 9-11% of new CPA/EE users other HC prescriptions were observed during the follow-up period (index date until end of calendar year) but without overlap with CPA/EE prescriptions and 61-63% of women did not have any other HC prescription record besides CPA/EE during the follow-up period.

10.4.2 Main results in THIN

The THIN study population for the interim analysis included 2,760 new CPA/EE users in 2011 and 2,923 new CPA/EE users in 2012. In 2014, for the final analysis, 2,341 new users were included. The proportions of new users in each year were 1.6 per 1,000 women in 2011, 1.6 per 1,000 women in 2012 and 1.3 per 1,000 women in 2014.

Most (55-56%) users were between 15 and 25 years old; the mean age at CPA/EE initiation was 23 in all study years. One year history was required for assessment of acne or other hyperandrogenic conditions; the median available history in the database was 12-13 years. Follow-up after the index date was restricted by the end of the study period (calendar year of index date) and therefore the median follow-up was 6 months. During this follow-up period, the majority of women (78-83%) had one uninterrupted episode of CPA/EE.

The median estimated duration of use per calendar year cohort was 3 months in 2011 and 2012 and 4 months in 2014.

The conditions considered treatment indications for CPA/EE and their prevalence were: acne (51% 2011, 54% in 2012, 55% in 2014), PCOS (6-7% over the study periods), hirsutism (3-4%), alopecia (1-2%) and seborrhoea (<0.5%). Individuals may have had more than one of these conditions. Of the remaining CPA/EE users, i.e. without any hyperandrogenic diagnosis, 4-5% had menstrual problems and another 20-23% (22% in 2011, 23% in 2012 and 20% in 2014) recently visited the GP for contraceptive management.

Among women with acne diagnosis recorded in the year prior to the index date, 83% in 2011 and 2012 and 84% in 2014 received acne treatment during that year. Among women without an acne diagnosis, 50% received acne treatment within the year prior to the index date in 2011, 54% in 2012 and 52% in 2014. The proportions of users with either acne diagnosis or treatment were thus 76% in 2011, 79% in 2012 and 78% in 2014.

Note that a major proportion of acne treatment was HC: 33-39% of women with an acne diagnosis and 37-41% of women without an acne diagnosis had used HC in the year before starting CPA/EE. Apart from HC, topical antibiotics (41-43%) and systemic antibiotics (38-47%) were the most widely used prescribed treatment among women with acne diagnosis as well as among women without acne diagnosis, although the proportions in the latter group were much lower: 9-13% and 10-13%, respectively.

Concomitant use of other HC was observed for 15 (1%) of new CPA/EE users in 2011 and less than 0.5% of new CPA/EE users in 2012 and 2014 (11 and 8 users, respectively). These concomitant users had completely overlapping treatment episodes of CPA/EE and HC. The median duration of concomitant use was 84 days in 2011 and 2012 and 77 days in 2014.

Another 4% of new CPA/EE users in 2011, 5% in 2012 and 4% in 2014 were potential concomitant users who started CPA/EE or other HC before the end date of the other drug prescription. The median duration of this potential overlap was 50 days in 2011 and 2012 and 34 days in 2014. Most concomitant use was observed with 28 days cycle HC.

For 4-5% of new CPA/EE users other HC prescriptions were observed during the follow-up period (index date until end of calendar year) but without overlap with CPA/EE prescriptions and 90-92% of women did not have any other HC prescription record besides CPA/EE during the follow-up period.

10.4.3 Main results in HSD

The HSD study population for the interim analysis included 495 new CPA/EE users in 2011 and 446 new CPA/EE users in 2012. In 2014, for the final analysis, 261 new users were included. The proportions of new users in each year were 0.8 per 1,000 women in 2011, 0. per 1,000 women in 2012 and 0.5 per 1,000 women in 2014.

Most users were between 15 and 25 years old; the mean age at CPA/EE initiation was 29 in all study years. One year history was required for assessment of acne or other hyperandrogenic conditions; the median available history in the database was 11-12 years. Follow-up after the index date was restricted by the end of the study period (calendar year of index date) and therefore the median follow-up was 6-7 months. During this follow-up period, the majority of women (63-67%) had one uninterrupted episode of CPA/EE.

Most prescriptions from the HSD GPs were Diane®-35 (82-83%). For CPA/EE prescriptions, the median estimated duration of use per calendar year cohort was 3 months in 2011 and 2012 and 2 months in 2014.

The conditions considered treatment indications for CPA/EE and their prevalence were: acne (14% 2011, 17% in 2012 and 14% in 2014), PCOS (3-6% over the study periods), hirsutism (3-4%), alopecia (2%) and seborrhoea (0%). Individuals may have had more than one of these conditions. Of the remaining CPA/EE users, i.e. without any hyperandrogenic diagnosis, 5-

6% had menstrual problems and another 7-11% (11% in 2011, 9% in 2012, and 7% in 2014) recently visited the GP for contraceptive management.

Among women with acne diagnosis recorded in the year prior to the index date, 19% in 2011, 26% in 2012 and 19% in 2014 received acne treatment during that year. Among women without an acne diagnosis, 6% received acne treatment within the year prior to the index date in 2011, 5% in 2012 and 5% in 2014. The proportions of users with either acne diagnosis or treatment were thus 19% in 2011, 21% in 2012 and 18% in 2014.

Systemic antibiotics were the most widely used prescribed treatment among women with acne diagnosis (4-13%) as well as among women without acne diagnosis (3-4%).

Concomitant use of other HC was observed for 1% of new CPA/EE users in 2011 and 2012 (4 and 3 users, respectively) and for 4 (2%) new CPA/EE users in 2014. These concomitant users had completely overlapping treatment episodes of CPA/EE and HC; the absolute numbers fell below the minimum of 5 required for summary statistics.

Another 4% of new CPA/EE users in 2011 and 2% in 2012 and 2014 were potential concomitant users who started CPA/EE or HC before the end date of the other drug prescription. The median duration of this potential overlap was 29 days in 2011 and 28 days in 2012. The absolute number in 2014 fell below the minimum of 5 required for summary statistics.

For 8-9% of new CPA/EE users other HC prescriptions were observed during the follow-up period (index date until end of calendar year) but without overlap with CPA/EE prescriptions and 87-89% of women did not have any other HC prescription record besides CPA/EE during the follow-up period.

10.5 Other analyses

Not applicable.

10.6 Adverse events/adverse reactions

Not applicable.

11 Discussion

11.1 Key results

11.1.1 Key results for PHARMO

A total of 7,876 new users of CPA/EE were identified in 2011, 7,526 new users were identified in 2012 and 1,401 new users were identified in 2014. The proportion of (new) users in 2014 had strongly (76%) decreased compared to 2011.

Recent diagnoses or treatment of acne and other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management was assessed among users with GP information available (1,415 in 2011, 1,359 in 2012 and 321 in 2014). A recent acne diagnosis was observed for 17% of new users in 2011, 16% in 2012 and 12% in 2014. Among users with no acne diagnosis, 40-45% had recently received acne treatment so in total 55% of users in 2011, 52% of users in 2012 and 47% of users in 2014 had a recent record of acne diagnosis or treatment. A diagnosis of hyperandrogenic conditions other than acne was observed for 3% in both study periods. Of the CPA/EE users without any hyperandrogenic diagnosis, 3% had menstrual problems and another 12-15% had an entry for contraceptive management. Similar results were observed in a summary of reports on thromboembolic adverse drug reactions associated with the use of CPA/EE submitted to the Netherlands Pharmacovigilance Centre up to April 2013. Out of 309 reports, 147 (47%) mentioned acne as primary indication, 122 (39%) mentioned contraception, 10 (3%) mentioned hirsutism and the remaining 30 reports mentioned other or unknown indications(11).

Some users (3% in 2011 and 2% in 2012 and 2014) had used CPA/EE in concomitance with other HC, as deducted from the prescription and dispensing records. Another group of users (25% in all study years) may have used CPA/EE in concomitance with other HC as their prescriptions overlapped, however as no new prescription was observed after the start of potential concomitant use, an actual switch was likely for these users. These results were similar in 2011, 2012 and 2014.

11.1.2 Key results for THIN

A total of 2,760 new users of CPA/EE were identified in 2011, 2,923 new users were identified in 2012 and 2,341 new users were identified in 2014. The proportion of (new) users slightly decreased (21%) in 2014.

A recent acne diagnosis was observed for 51% of new users in 2011, 54% in 2012 and 55% in 2014. Among users with no acne diagnosis, 50-54% had recently received acne treatment so

in total 76% of users in 2011, 79% of users in 2012 and 78% of users in 2014 had a recent record of acne diagnosis or treatment. Similar results were observed in a prior research project where the diagnosis or indication recorded at the time of prescription of cyproterone acetate/ethinylestradiol (CPA/EE) was determined. In that study, there were a total of 80% of women with acne, 5% with hirsutism and 9% had a record only for contraception in 2010 (not yet published)

Few users (1% in 2011 and less than 0.5% in 2012 and 2014) had used CPA/EE in concomitance with other HC, as deducted from the prescription records. Another group of users (ranged from 2-4%) may have used CPA/EE in concomitance with other HC as their prescriptions overlapped, however as no new prescription was observed after the start of potential concomitant use, an actual switch was likely for these users. These results were similar in 2011, 2012 and 2014. A prior study on the topic with the same data source showed that among women who initiated the treatment with oral contraceptives (any), a low proportion (<10%) of combined oral contraceptive pill users switched to an alternative brand during the first year, and 9.0% switched to a method other than combined oral contraceptive pill (i.e., progestogen-only pill, injections, patches, or LARCs) during the first year of use (6). These data are in line with the current results.

11.1.3 Key results for HSD

A total of 495 new users of CPA/EE were identified in 2011, 446 new users were identified in 2012 and 261 new users were identified in 2014. The number of (new) users in 2014 had strongly decreased (53%) compared to 2011.

A recent acne diagnosis was observed for 14% of new users in 2011, 17% of new users in 2012 and 14% of new users in 2014. Among users with no acne diagnosis, 5-6% had recently received acne treatment so in total 19% of the users in 2011, 21% of the users in 2012 and 18% of the users in 2014 had a recent record of acne diagnosis or treatment.

Some users (1% in 2011 and 2012 and 2% in 2014) had used CPA/EE in concomitance with HC, as deducted from the prescription records. Another group of users (ranged from 2-4%) may have used CPA/EE in concomitance with HC as their prescriptions overlapped, however as no new prescription was observed after the start of potential concomitant use, an actual switch was likely for these users.

11.2 Limitations

Some limitations should be considered in the present study. Reliability of the results is dependent on the quality and completeness of the recording of patient data, and this might be variable between the three different healthcare databases as suggested in the difference of the main results.

Limitations regarding exposure

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, the databases provide detailed information on prescribed and/or dispensed medications but not on the actual use of the medications by patients. Thus, individuals 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 HC (intra-uterine devices, injections and implants) may have been misclassified since removal dates are not consistently captured in the databases. To be eligible for inclusion in our study, women were requested to have at least one year recorded history in the database. This eligibility criterion may have resulted into some misclassification of exposure of these devices in both directions, potential for false negatives (underreported use (earlier than one year prior start of CPA/EE use) or false positives (removal or ended life cycle of these devices at the time of start of CPA/EE use or during the year after). However, the use of LARC is low especially among the younger users (9). Another limitation of the assessment of medication use from databases is that over-the-counter medications are usually not recorded. As over-the-counter 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 9.4), in GP databases only GP prescriptions are recorded, not specialist prescriptions, e.g. from gynaecologists (for CPA/EE and other HC) or dermatologists (for acne treatment). Completeness of recording of refill dispensings in the GP (prescription) database varies by database. In THIN and HSD which do not capture specialist prescriptions, the precision of the index date and the magnitude of underestimating exposure (and thereby concomitant use) depends on the role of the specialist in prescribing CPA/EE and other HC. In the UK, the GP is cited as the most common provider of contraceptives In THIN, an estimated 24% of LARC users were administered the device at a family planning clinic or hospital outpatient clinic, showing that information regarding LARC use outside general practice is received and recorded by GPs although it is not possible to determine the proportion of data that are captured (7). In HSD, the specialist might have more involvement in HC prescription since no prescription of LARC is observed.

Limitations regarding diagnoses

Databases of electronic medical records are restricted to information recorded to serve the purpose of the medical record: primary care, claims, etc. Because these databases are not designed to perform research, underreporting or incomplete reporting of events may occur. It is therefore difficult to estimate with complete precision the diagnosis for which the drug is

prescribed, the level of 'on-label' or 'off-label' prescribing (i.e. diagnoses that have not received regulatory approval as indication for use). For acne and other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management, there is no incentive for GPs to accurately monitor and record diagnoses and outcomes like there is, for example, for diabetes in PHARMO and THIN. Similar explanation can be raised for HSD; all these conditions can be encountered by GPs early on, while these patients are subsequently followed by specialists. This underreporting may limit the inference about assumed indication for use. As the indication for use is not recorded for most of the prescriptions, the interpretation of the indication depends on concomitantly recorded diagnoses. For the current study diagnoses of acne and other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management were identified from up to one year before the index date, which might not reflect the actual underlying indication for the prescription of the CPA/EE in some instances, especially if GPs include this data beyond the index date. In addition, diagnoses recorded more than one year before the index date were not included in the analysis. In THIN, where the diagnosis coding was most complete, the proportion of women with an entry of acne was about 50% both in 2011 and 2012. Yet, when evaluating acne treatment stratified among women with and without acne, 80% of women with acne received at least one treatment indicated for acne within the year prior to CPA/EE. In PHARMO and HSD low proportions of all conditions were observed indicating substantial underreporting of acne and other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management in these databases.

Protocol deviations

A minor deviation from the Study Protocol was about the definition of 'new' CPA/EE users which was applied slightly different in the databases. Apart from the users with a prescription in the 365 days preceding the index date, PHARMO also excluded users whose prescription was earlier but not expired before 365 days prior to the index date and THIN also excluded users with a prescription any time in the preceding calendar year. As these exclusions applied to a small number of users (~100 women) and are not likely to be selective, the protocol deviations are not expected to affect the study results.

Another deviation from the Study Protocol was that 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. Concatenation of prescriptions, which is done to create episodes, may have pushed HC exposure before index date forward and therefore created more overlap with the first CPA/EE episode. Potentially, this deviation from the Study Protocol may have resulted in relatively less overlap in THIN in terms of the proportions and durations of concomitant (potential) use. Both methods are however based on assumptions of the actual use.

11.3 Interpretation

This drug utilization study was initiated in 2013, following the recommendation of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) to implement risk minimization measures to minimize the risk of thromboembolism among users of CPA/EE. According to these recommendations, the drug should be used solely in the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of reproductive age. CPA/EE should only be used for the treatment of acne when alternative treatments, such as topical therapy and systemic antibiotic treatment, have failed.

The study was performed in three databases, from different countries but also different healthcare settings. The results were therefore presented by database and without the objective to compare the results between databases, only between study years. The following sections do discuss the databases together, in order to provide the general interpretation on user characteristics (section 11.3.1) and also to provide some background on the different databases and settings and implications for the results specifically for concomitant use (section 11.3.2).

11.3.1 User characteristics

The current study shows that, among new users of CPA/EE, most women fell in the category of 15-34 years of age in all study years and databases, with a higher proportion of older women in HSD. Follow up time from index date (first CPA/EE prescription) to end of each calendar period was, on average, 6 months in all databases, a sufficient time interval to measure treatment patterns. Number of CPA/EE episodes was counted during the follow up period of each calendar year, as was the overall duration of CPA/EE treatment.

The proportions of users diagnosed with any hyperandrogenic condition were stable across the study years. Observed proportions were 16-20% in PHARMO, 61-63% in THIN and 22-24% in HSD. The most frequently reported condition was acne and when also considering acne treatment, the proportions of women with any record of acne (diagnosis an/or treatment) were close to 80% for all calendar years in THIN, 47-55% in PHARMO, and 18-21% in HSD. The current results suggest that in THIN the vast majority of women starting treatment with CPA/EE have a hyperandrogenic condition in compliance with the labelled indications for CPA/EE. This was observed in all study years. In PHARMO and HSD, the recorded diagnoses reflect the recommended CPA/EE use to a lesser extent which for e.g. the Netherlands corresponds to previous observations (11).

In all three databases, up to 10% of users had diagnoses of other hyperandrogenic conditions and few women had a record of menstrual problems or GP consultations for contraceptive management in the year before start of CPA/EE use. There is a substantial chance of

underreporting in this study as discussed in the previous section and in addition specialist prescriptions were not captured in THIN and HSD. Assuming that the completeness of information on acne diagnosis and treatment and diagnoses of other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management was similar in 2014, conclusions may be drawn on the relative proportions in 2011, 2012 and 2014, but not on the absolute proportions in one study period.

11.3.2 Concomitant use

CPA/EE also acts as a hormonal contraceptive. Women should not take this medicine in combination with other HC as this would expose women to an excessive hormonal dose which is a safety concern. A small proportion of users were categorized as concomitant users in all databases. A larger proportion, particularly in PHARMO, was classified as potential concomitant users. Several differences exist between the countries/databases which might have led to large differences in the estimated proportions of potential concomitant use. There are differences in 1) completeness of information about HC use in each database, 2) the average durations of prescriptions in each database and 3) prevalence of CPA/EE and HC use in the source populations. In addition, local guidelines, clinical recommendations and regulatory advices in each country may differ and lead to different patterns of contraceptive management. Before we elaborate on these points it should be emphasized that potential concomitant use was defined as overlapping prescriptions of CPA/EE and other HC, but without a new prescription of the first drug after initiation of the second. As the prescription records only reflect what was dispensed (PHARMO) or prescribed (THIN and HSD) and not what was actually consumed, the remaining doses of the first drug may not have been used. In other words, potential concomitant users were likely switchers from other HC to CPA/EE or vice versa.

With regard to the completeness of information about CPA/EE and other HC use: this was studied in the Out-patient Pharmacy Database in PHARMO which included specialist prescriptions as well, while HSD and THIN include only GP records. Note however that in THIN, good coverage of HC prescription has been observed (7).

The likelihood of overlapping prescriptions, regardless of whether there was actual concomitant use, is larger when the prescriptions are longer. The average durations of prescriptions in each database were different. The overlap was presented in cycles, which are 28 days for CPA/EE and most other HC. The median HC or CPA/EE prescription durations were 3-6 cycles in PHARMO, 3-4 cycles in THIN and 2 cycles in HSD. Assuming that potential concomitant users are actual switchers, this means that either a larger part of the remaining doses was not consumed, or the actual start date of the second drug was later.

Finally, with regard to the prevalence of CPA/EE and HC use in the source populations, we observed that 37-39% of new CPA/EE users in PHARMO had an “other HC” prescription

within 365 days before the index date until end of follow-up (regardless of overlap), while only 11-13% in HSD and 8-10% in THIN had an “other HC” prescription. The likelihood of overlapping prescriptions also depends on the population proportions on each drug. In a previous study of oral contraceptive use in 2009-2010 in the same databases (study commissioned and funded by the EMA under service contract number EMA/2011/37/CN (oral contraceptives)(12), the observed use of oral contraceptives in the source population was also clearly lower in HSD than in PHARMO. The proportion of oral contraceptive users in THIN was similar. The yearly incidence of CPA/EE use in the current study was highest in PHARMO: in 2011 2.8 per 1,000 women started using CPA/EE and corresponding numbers were 1.6 per 1,000 in THIN and 0.8 per 1,000 in HSD.

Despite these differences between the databases, the proportions of concomitant use were low in all databases. Also note that the estimates were actually concomitant prescriptions rather than actual use, which may even be lower due to delayed start dates or non-consumed pills of the first drug. Especially for potential concomitant use this had probably led to overestimation to an extent as large as the amount of missing information about delayed start dates or non-consumed pills.

11.4 Generalisability

The study cohorts included new CPA/EE users from population-based healthcare databases. The HSD and THIN cohorts were GP-based and the PHARMO cohorts were pharmacy-based. The GP is a gatekeeper in all three countries and as such the source populations are assumed to be representative of the general population. As observed in the PHARMO cohorts, most CPA/EE prescriptions are issued by the GP, however this proportion may vary between countries. For prescriptions issued by specialists, the GP in general continues the refill prescriptions. Therefore, also the user cohorts are assumed to be representative of the actual user population.

12 Other information

Not applicable.

13 Conclusion

A descriptive analysis was performed of CPA/EE use in 2011, 2012 and 2014 in three separate databases. The study periods represent the times before and after the referral procedure in which MAHs were required to implement further measures to minimize the risk of thromboembolism among CPA/EE users. During both study periods, limited information on acne diagnosis, diagnoses of other hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management or recent acne treatment was observed in the

PHARMO and HSD databases. This might be due to underreporting; in the THIN database the majority of CPA/EE users had a recent record of acne diagnosis or treatment.

Concomitant use of CPA/EE and other HC was observed for a small proportion of users during all calendar years in the study.

Apart from a strong overall reduction of CPA/EE use in PHARMO and HSD and a slight decrease in the use in THIN, no major difference was observed in any of the databases between proportions diagnosed with acne or other hyperandrogenic conditions, or with recent acne treatment, or with concomitant use of HC was observed between the study periods before and after the referral procedure.

14 References

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Appendices

Annex 1 List of stand-alone documents

Annex Table 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 oestrogen	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	

Substance	ATC code
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.

Annex Table 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;

Gemscript	Descriptor
	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

Gemscript	Descriptor
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

Gemscript	Descriptor
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

Gemscript	Descriptor
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	Subcutaneous contraceptive implant 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

Annex Table 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 were selected based on local guidelines as described in section 9.4.2.

Annex Table 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

Gemscript	Descriptor
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

Gemscript	Descriptor
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

Gemscript	Descriptor
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

Gemscript	Descriptor
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

Gemscript	Descriptor
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

Gemscript	Descriptor
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

Gemscript	Descriptor
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

Gemscript	Descriptor
99683997	Erythromycin 500mg e/c tablet

Annex Table 5 Codes of diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management 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

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

Annex Table 6 Read codes of diagnoses of hyperandrogenic conditions, menstrual problems or GP consultations for contraceptive management 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

Read code	Descriptor
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

Read code	Descriptor
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

Read code	Descriptor
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

Read code	Descriptor
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

Read code	Descriptor
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

Read code	Descriptor
Seborrhoea	
M263.00	Seborrhoea
M263000	Seborrhoea corporis
M263100	Seborrhoea faciei
M263200	Seborrhoea nasi
M263300	Seborrhoea oleosa
M263z00	Seborrhoea NOS
M263z00	[X]Other seborrheic dermatitis

Signature Page - Epidemiology

Study Title:	*Drug utilization study of cyproterone/ethinylestradiol (Diane®-35 and generics) in the Netherlands, UK and Italy*
Product:	*Diane®-35 and its generics*
IMPACT Study Number:	*17660*
Study Type:	*PASS*
EU PAS Register Number:	*ENCEPP/SDPP/8412*
Development phase:	*Post-Authorization*
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature: 15.03.2016 ,

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EU PAS Register Number:	*ENCEPP/SDPP/8412*
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Development phase:	*Post-Authorization*
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Study Type:	*PASS*
EU PAS Register Number:	*ENCEPP/SDPP/8412*
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EU PAS Register Number:	*ENCEPP/SDPP/8412*
Development phase:	*Post-Authorization*
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Date, Signature: 10 March, _____

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Study Type:	*PASS*
EU PAS Register Number:	*ENCEPP/SDPP/8412*
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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EU PAS Register Number:	*ENCEPP/SDPP/8412*
Development phase:	*Post-Authorization*
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature: 10-03-2016, _____

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

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Study Type:	*PASS*
EU PAS Register Number:	*ENCEPP/SDPP/8412*
Development phase:	*Post-Authorization*
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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Date, Signature: March 18th, 2016 Michael Kayser

Confidentiality statement: