1 December 2016
EMA/101714/2017
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC non-interventional imposed PASS final study report assessment report

Active substance: cyproterone/ethinylestradiol

Procedure no.: EMEA/H/N/PSR/J/0003

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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

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

1. Background information on the procedure

In order to fulfil the obligation to submit the results of an imposed non-interventional PASS in accordance with Article 107p of Directive 2001/83/EC, Bayer Pharma AG/consortium submitted on 29 March 2016 a joint database drug utilisation final study report to the European Medicines Agency (EMA) for cyproterone/ethinylestradiol.

For an overview of the nationally authorised products covered in the context of this joint final study report, please see appendix to this assessment report.

PASS information

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	23 March 2016
EU PAS register number	ENCEPP/SDPP/8412
Active substance	Cyproterone/ethinylestradiol (CPA/EE)
Medicinal product	Diane-35 and generics
Product reference	n/a
Procedure number	EMEA/H/N/PSR/J/0003
Marketing authorisation holder(s)	See appendix
Joint PASS	Yes
MAH(s) contact	
Research question and objectives	The study objectives are to characterize new users of CPA/EE in 2011/2012 and in 2014 according to demographics, treatment characteristics, previous diagnosis of acne, hirsutism or other hyperandrogenic conditions, previous acne treatment and (concomitant) use of hormonal contraceptives. A secondary objective is to compare patient and treatment characteristics between January 1, 2011 and December 31, 2012 and January 1, 2014 and December 31, 2014.
Country(-ies) of study	Netherlands, United Kingdom, Italy

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2. Final assessment conclusions and actions

Diane 35 (and generics) is a combined medicinal product containing the active substances cyproterone acetate (CPA) 2 mg and ethinylestradiol (EE) 0.035 mg. The first marketing authorization for cyproterone/ethinylestradiol (CPA/EE) was granted in Germany in 1985.

CPA/EE was the subject of an Article 107i referral procedure initiated by the French Medicine Agency, ANSM, in February 2013 to review the risk of thromboembolism in its users, following a national review which highlighted serious thromboembolic events and extensive off-label use of this medicine as a contraceptive only. 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 outweigh the risks, provided that several measures are taken to minimize the risk of thromboembolism. During the referral the indication of this product was harmonised across the EU and is now as follows:

"*Treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age. For the treatment of acne, CPA/EE should only be used after topical therapy or systemic antibiotic treatments have failed.*
Since CPA/EE is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3)"

The new indication was more restrictive compared to indication before the referral since CPA/EE was not always used as second line for acne in some countries.

In order to minimise the risk of thromboembolic events occurring with CPA/EE, apart from the restriction in the indication, additional risk minimisation measures were implemented. These included a Direct Healthcare Professional Communication (DHPC) and educational materials for prescribers and patients (i.e. prescribers checklist and patients information cards) highlighting the risks as well as warnings on thromboembolism.

In addition, imposed studies were requested to be conducted by MAHs to evaluate the effectiveness of risk minimisation measures:

- One post-authorisation safety study (PASS, multinational, cross-sectional survey) designed to measure physician knowledge and understanding of key safety information for CPA/EE, and to evaluate effectiveness or risk minimisation with respect to ATE/VTE events.
- Two drug utilisation studies to evaluate effectiveness with regards to reduction of off label use:
    - Survey Drug Utilisation Study (DUS, multinational, cross-sectional, survey): aimed to characterize the prescribing behaviours for CPA/EE in 5 European countries (Austria, Czech Republic, France, Netherlands, and Spain), which includes the characterization of

prescribing indications for CPA/EE and the use of CPA/EE according to the harmonized label. The study had a special focus on the clinical decision-making process.

- Database DUS (retrospective, multinational, database-based study): aimed to evaluate user demographics and treatment characteristics during 2011-2012 and 2014 (after referral) and compare these to observe any change in prescribing behaviour.

It was agreed that there was a need for both a database study and a survey and that these two approaches should be complementary. The database study would provide insight into user characteristics and the indication for prescribing in three countries, whereas the survey would provide insight into determinants of prescribing not captured in databases and in countries where no healthcare databases were available for these analyses.

This assessment report summarises the results of the database DUS, which was conducted in three national databases in Italy (HSD), the Netherlands (PHARMO) and UK (THIN). The main study objective was to assess the following characteristics among new users of CPA/EE: user demographics; treatment characteristics; recent diagnosis of acne, hirsutism, other hyperandrogenic conditions, menstrual problems or consultations with general practitioners (GP) for contraceptive management; recent acne treatment and (concomitant) use of hormonal contraceptives (HC). The main outcomes investigated were the overall use, the registered diagnosis for use, concomitant prescription with other contraceptives and off label use, particularly use as a contraceptive.

In the Netherlands the proportion of new users in 2014 (1,401 users) had strongly decreased compared to 2011 (7,876 users). The decrease in the Netherlands may have been driven by the public CPA/EE discussion at the time of the referral and the fact that reimbursement for this product ceased. There was also a major decrease in number of users in Italy from 2011 (495 users) to 2014 (261 users).

In new users with a registered diagnosis, data shows that CPA/EE is mostly prescribed for hyperandrogenic conditions (out of which acne was predominant at above 75%).

The concomitant prescription of CPA/EE with other hormonal contraceptives was observed to have decreased by almost 50% in THIN and 66% in PHARMO from 2011 to 2014. Concomitant prescription should not be understood to be synonymous with concomitant use (users may stop using other hormonal contraceptives once CPA/EE is started). The concomitant prescription with other hormonal contraceptives decreased only in absolute numbers, but the percentage did not substantially change across the study years, suggesting an overall decrease in use, not necessarily a change in prescribing pattern. The percentage of concomitant use (0.5-3%) is low and consistent with what was observed in the survey DUS.

With regards to prescription of CPA/EE for contraceptive management, a decrease in the prescription was observed in all three databases. The percentage of CPA/EE use as a contraceptive (7-20%) is similar to the one obtained from the survey DUS, increasing the credibility of this estimate.

Since the databases do not allow for entry multiple diagnoses, patients might have been prescribed CPA/EE for other reasons in addition to contraception. Therefore, it cannot be fully ascertained whether, in these patients, CPA/EE was used solely for contraception.

Based only on the results from the database DUS, the effectiveness of risk minimisation measures cannot be fully evaluated, as misclassification of both outcomes and exposure might have occurred. Due to these limitations, the survey DUS was performed in addition, providing data from a different perspective and supplement those instances where the current database study had limitations.

In conclusion, this study has shown that CPA/EE is mostly used for hyperandrogenic conditions (usually acne), therefore according to the label. The use of CPA/EE purely for contraception as well as concomitant use of CPA/EE with other hormonal contraceptives was only observed for a small proportion of users during all calendar years. Overall, the DUS has shown that CPA/EE use following the outcome of the referral decreased markedly in the Netherlands and slightly in Italy.

In order to further monitor the observed concomitant use of CPA/EE with other hormonal contraceptives as part of additional pharmacovigilance activities, the PRAC agreed on the need to perform a follow-up review of available drug utilisation data from electronic healthcare record databases comparing the patterns of concomitant use over time and submission of these results in Q1 2019.

The same methodology and mode of results should be presented as per current database DUS protocol, for facilitating the comparison of patterns of use over time. For the same reason, use of the same databases is preferred. Should the MAH wish to change the databases in which the follow up study is conducted this could also be accepted provided that data are collected on both the new time period and the previous period.

The results should be submitted by the MAH of the originator product as part of a Works-Sharing (WS) variation to be assessed by the relevant national competent authorities. Generic MAHs are not requested to perform this follow-up review since no additional information would be gathered using the same databases.

In addition, this follow-up review should be included in the RMP for the MAH of the originator product as a non-imposed study (category 3).

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

The joint database drug utilisation final study report submitted by the MAHs, together with the joint survey database drug utilisation final study report submitted by the MAHs as a separate procedure (EMEA/H/N/PSR/J/0005), complies with their obligation to conduct a database drug utilisation study to characterise prescribing practices for the medicinal product during typical clinical use in representative groups of prescribers and to assess the main reason for prescription, as imposed during the Article 107i procedure EMA/H/A-107i/1357 for cyproterone/ethinylestradiol containing products.

Therefore, in view of available data regarding the joint database drug utilisation final study report, together with the joint database drug utilisation final study report submitted as a separate procedure (EMEA/H/N/PSR/J/0005), the PRAC considered that changes to the conditions of the marketing authorisation were warranted.

3. Final Recommendations

Based on the PRAC review of the joint database drug utilisation final study report version 1.0 dated 23 March 2016 and taking into account the joint survey drug utilisation final study report submitted as a separate procedure (EMEA/H/N/PSR/J/0005), the PRAC considers that:

☒ the risk-benefit balance of medicinal products containing the active substance cyproterone/ethinylestradiol concerned by the joint database drug utilisation final study report remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as

follows:

The following changes to the conditions of the marketing authorisation(s) of medicinal products containing the active substance cyproterone/ethinylestradiol concerned by the joint database drug utilisation final study report are recommended:

The marketing authorisation holder (s) shall remove the below condition:

The MAH(s) should provide within the risk management plan submission, a protocol for the drug utilisation study to characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription. Final study report by:	31 July 2015

In addition, the MAH for the innovator product Diane 35 (Bayer) should address the following issues:

- Submission to the relevant National Competent Authorities of a follow-up review of available drug utilisation data from electronic healthcare record databases comparing the patterns of concomitant use over time and submission of these results in Q1 2019.

The same methodology and mode of results should be presented as per current database DUS protocol, for facilitating the comparison of patterns of use over time. For the same reason, use of the same databases is preferred. Should the MAH wish to change the databases in which the follow up study is conducted this could also be accepted provided that data are collected on both the new time period and the previous period.

- Update the RMP to include the requested follow-up review of drug utilisation data as a category 3 study, and submission to the relevant National Competent Authorities within 6 months following adoption by CMDh.

4. Other considerations

☒ The recommendations proposed by the PRAC in this report merit careful consideration by the CMDh, as they propose substantial modifications in the conditions of the marketing authorisation(s) of medicinal products containing the active substance cyproterone/ethinylestradiol concerned by the joint database drug utilisation final study report.

Where this imposed PASS is the only criteria for additional monitoring, the deletion of the black symbol and the related statement in the product information would be warranted.