1 December 2016
EMA/101726/2017
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC non-interventional imposed PASS final study report assessment report

Cyproterone/ethinylestradiol

Active substance: cyproterone/ethinylestradiol

Procedure no.: EMEA/H/N/PSR/J/0005

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

ADB Administrative Database

ADR Adverse Drug Reaction

ANSM Agence nationale de sécurité du médicament et des produits de santé

ATC Anatomical Therapeutic Chemical Classification System

CCTIRS Comité consultative sur le traitement de l'information en matière de recherche dans le domaine de la santé

CHC Combined Hormonal Contraceptive

CMDh Coordination Group for Mutual Recognition and Decentralized Procedures – Human

CNIL Commission nationale de l'information et des libertés

CNOM Conseil national de l'Ordre des médicins

CPA Cyproterone Acetate

DUS Drug Utilization Study

EE Ethinylestradiol

EMA European Medicines Agency

ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

FIGO International Federation of Gynecology and Obstetrics

GEP Good Epidemiological Practices

GP General Practitioner

GPP Good Pharmacoepidemiology Practices

GVP Good Pharmacovigilance Practice

GXP Good Practice Guidelines

ICMJE International Committee on Medical Journal Editors

ISPE International Society for Pharmacoepidemiology

MAH Marketing Authorization Holder

OTC Over-the-counter

PCOS Polycystic Ovary Syndrome

PRAC Pharmacovigilance Risk Assessment Committee

SAE Serious Adverse Event

SDB Study Database

SOP Standard Operating Procedure

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 30 May 2016 a joint survey drug utilization 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 final study report, please see appendix to this assessment report.

PASS information

Title	Final study report on the survey Drug Utilization Study (DUS) with Cyproterone Acetate + ethinylestradiol
Version identifier of the final study report	01
Date of last version of the final study report	23 May 2016
EU PAS register number	ENCEPP/SDPP/8365
Active substance	Antiandrogens and estrogens ATC code: G03HB01
Medicinal product	Diane-35 and its generics: coated tablets 0.035 mg ethinylestradiol, 2.0 mg cyproterone acetate (CPA/EE)
Product reference	Not applicable
Procedure number	EMEA/H/N/PSR/J/0005
Marketing authorisation holder(s)	Bayer HealthCare Pharmaceuticals On behalf of a group of MAHs
Joint PASS	Yes
MAH(s) contact	Müllerstraße 178 13353 Berlin Germany
Research question and objectives	This drug utilization study is designed to compile the reasons and specific indications for the prescription of CPA/EE. The primary objective of the study is to characterize the prescribing behaviors for CPA/EE in 5 European countries including: • prescription indications for CPA/EE • use of CPA/EE in accordance with the updated label • concomitant use of CPA/EE and CHCs • second-line treatment with CPA/EE for the indication acne
Country(-ies) of study	Austria, Czech Republic, France, The Netherlands, and Spain
Author	Klaas Heinemann, MD, PhD, MBA, MSc

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 authorisation 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 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 survey DUS, a cross-sectional survey conducted in five European countries, Austria, Czech Republic, The Netherlands, France and Spain. The study objectives included the characterization of the prescribing behaviours for: prescription indications for CPA/EE; use of CPA/EE in accordance with the updated label; concomitant use of CPA/EE and other hormonal contraceptives (HCs); second-line treatment with CPA/EE for the indication acne.

One of the major findings was the difficulty in the recruitment of physicians for this survey. The study participation rate was much lower than expected, with the final sample comprising a total of 1,513 patients recruited by 120 physicians (70% lower than estimated). This impacted the precision of the estimates, however since 3 out of 5 countries met the predefined precision thresholds, the overall data is considered valid and sufficiently accurate for the study to meet its objectives.

This report shows that CPA/EE is in general used according to the label. In total, 83.3% (n = 1,261) of all prescriptions were issued for patients with at least one condition within the context of a pathophysiology associated with androgenicity of which acne was the most common diagnosis (65.6%, n =993). The highest adherence to indication was observed in France, while this was the lowest in Austria. Importantly, this result was consistently observed in the database DUS evaluating user characteristics and also in the PASS evaluating physician's knowledge. However, 34.5% of the total study population had a diagnosis of moderate to severe acne with "previous topical and/or systemic antibiotic treatment" and/or hirsutism. It is important to consider that the information about previous acne treatments is likely to be incomplete because of recall bias, especially for OTC treatments, cosmeceuticals and special therapies such as light-therapies.

In 16.3% of cases, CPA/EE was prescribed for contraception only (range 8-22%), which is considered as off-label use according to the current product information. The data is similar to the results from the database DUS, where the proportion ranged from 7% in Italy to 20% in UK. Since in the survey DUS, physicians were specifically asked about reasons for prescription, and they could select more than one option, it is more likely, than in the database DUS, that these results provide an adequate reflection of actual clinical practice. The gynaecologists were also more likely to prescribe CPA/EE as first line treatment for acne compared to GPs and dermatologists. This finding should however be interpreted with some caution, since gynaecologists may have been less likely to comprehensively report all previous treatments for acne or they might treat patients referred from GPs who were previously treated.

The instances of concomitant use with other contraceptives with CPA/EE was 2.9% (n = 44) and was driven mainly by data from Czech Republic (3.7%, n = 21) and Spain (3.4%, n = 21). The other three countries have either no prescriptions or a very low number (n=2 patients in France). This percentage is similar to what was observed in the database study (less than 3% of concomitant use with other hormonal contraceptives shown in any of the 3 databases used in the database DUS). Consistency of results increases certainty regarding these figures. It is important to consider that these patients reported the use of other hormonal contraceptives at the time the CPA/EE is prescribed. It cannot be assumed that all of them would be using other hormonal contraceptives along with CPA/EE administration. They might stop using other hormonal contraceptive once CPA/EE is started.

It appears that gynaecologists prescribed concomitant contraceptives with CPA/EE twice as much as other specialties. This is surprising given their presumed expertise in hormonal treatments and

products. Lack of supplementary data precluded investigation of the causes for this observed behaviour.

Altogether, on an aggregate level, the study is informative with regard to the clinical scenario with respect to the prescription of CPA/EE by gynaecologists, dermatologists, and GPs. Most prescriptions were for one of the conditions whose pathophysiology is associated with an androgenic action.

Since this survey is based on the willingness of physicians to provide information about their reasons for prescribing CPA/EE, the data cannot indicate whether there is a difference in prescribing habits between participating and non-participating physicians, so a degree of bias cannot be excluded and should be taken into account when interpreting the results.

Because the study did not reach the original goal of 1,000 patients or be recruited per country, the sample sizes are not representative of all the individual countries. Nevertheless, because the acquired information came directly from the prescribers, the 1,513 evaluated prescriptions can provide some insight into the prescribing habits of European physicians.

Despite these limitations, the study provided an overall picture of the CPA/EE use by the prescribing physicians. The results show that the risk minimisation measures introduced with the referral were effective in reducing the number of patients exposed to CPA/EE for the incorrect indication.

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

The joint survey drug utilisation final study report submitted by the MAHs, together with the joint database drug utilisation final study report submitted by the MAHs as a separate procedure (EMEA/H/N/PSR/J/0003), complies with their obligation to conduct a drug utilisation study to characterise prescribing practices for the medicinal product during typical and 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 survey 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/0003), 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 survey drug utilisation final study report version 1.0 dated 23 May 2016, and taking into account the joint database drug utilisation final study report submitted as a separate procedure (EMEA/H/N/PSR/J/0003), the PRAC considers that:

☒ the risk-benefit balance of medicinal products containing the active substance cyproterone/ethinylestradiol concerned by the joint survey 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 survey 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

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 survey 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.