1 December 2016
EMA/101741/2017
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/0006

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List of abbreviations

ATE arterial thromboembolism

Bayer Bayer Pharma AG

CI confidence interval

CPA/EE cyproterone acetate 2 mg/ethinylestradiol 35 µg

CRM Customer Relationship Management

DHPC Dear Healthcare Professional Communication

DHPL Dear Healthcare Provider Letter

EMA European Medicines Agency

ENCePP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

EU European Union

GP general practitioner

MAH marketing authorisation holder

NCA National Competent Authority

PASS Post-Authorisation Safety Study

PRAC Pharmacovigilance Risk Assessment Committee

PIL Patient Information Leaflet

RMM Risk Minimization Measures

RTI-HS RTI Health Solutions

SmPC Summary of Product Characteristics

VTE venous thromboembolism

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 June 2016 a PASS final study report to the European Medicines Agency (EMA) for cyproterone/ethinylestradiol (CPA/EE).

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	Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	31 May 2016
EU PAS register number	ENCEPP/SDPP/9312
Active substance	INN: cyproterone acetate 2 mg/ethinylestradiol 35 µg; ATC code: G03HB01
Medicinal product	Diane-35 and its generics (CPA/EE)
Product reference	Not applicable
Procedure number	EMEA/H/N/PSR/J/0006
Marketing authorisation holder(s)	Bayer Pharma AG on behalf of a group of marketing authorisation holders
Joint PASS	Yes

Research question and objectives	The primary objective of this study was to measure physician knowledge and understanding of the key information included in the educational material for Diane-35 and generics. Specifically, the following objectives were addressed: ▪ Investigation of whether physicians have received any educational material related to CPA/EE ▪ Assessment of physicians' knowledge and understanding of key safety information pertaining to the patient information card ▪ Assessment of physicians' knowledge and understanding of key safety information included in the prescribers' checklist pertaining to the following areas: – Contraindications relevant to thromboembolism
Country(-ies) of study	Austria, the Czech Republic, France, the Netherlands, and Spain
Authors	Kimberly Davis, MS, BS Elizabeth Andrews, PhD, MPH RTI Health Solutions, Research Triangle Park, North Carolina

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 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 (DUS) 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.

This assessment report summarises the results of the PASS, a cross-sectional study conducted in five countries, Austria, Czech Republic, The Netherlands, France and Spain whose objective was to assess the physician knowledge and understanding of the key information in the educational materials distributed to healthcare professionals and patients, as an outcome of the referral, i.e. investigation of whether physicians had received any educational materials related to CPA/EE; and the physicians' knowledge and understanding of key safety information included in the prescribers' checklist pertaining to the following areas:

- Contraindications relevant to thromboembolism;

- Risk factors for thromboembolism;

- Signs and symptoms of thromboembolism.

The study results indicated that there was a low response rate of approximately 7% across all participating countries (a total of 11,102 physicians were invited to participate, of which 1,347 responded but only 759 physicians completed the questionnaire). It is not uncommon for the response rate to be below 10% for these surveys evaluating program effectiveness. The low rate observed in this study is also consistent with external studies as well as internal studies. It has been noted in the literature that participation rates have been decreasing over the past 30 years with even more decline in recent years.

In the study under discussion, more than half (51%) of physicians who completed the questionnaire, reported receiving at least one of the three CPA/EE materials. The proportion of physicians who reported to have received the DHPC ranged, according to the countries, from 17.8 % to 86.7%, 7.4% to 41% for the Patient card and 9% to 27.5% for Prescriber Checklist. This falls within the ranges reported in literature. The relatively low level of reported receipt of the physician education materials may reflect poor recall, whether the material had indeed been received, or various reasons for not receiving the educational materials. Most of the physicians (81.0%) who received at least one of the CPA/EE materials found it helpful or extremely helpful.

Variability across countries may reflect inherent differences in physician behaviour or different intensity of the educational efforts. Furthermore, in some of these countries, the agreed targeted specialties for the distribution of CPA/EE materials were different from the studied specialties i.e. no distribution to GPs in Austria and Czech Republic and targeted distribution to dermatologists only in Spain which has contributed to dilute the results further.

The knowledge and understanding of the key information among those physicians who did not report receiving any additional materials was similar to those who received educational materials, especially regarding the knowledge of the risk factors for VTE and the contraindications , as well as the restricted indication for acne in the revised product information, were well and widely known. This high level of knowledge among treating physicians suggests that the key safety information through other sources (e.g., product label, seminars or symposia) is available and used. The physicians' knowledge of the risk of VTE/ATE with CPA/EE use was high. The physicians were well aware of the signs and symptoms of thrombosis as well as the risk factors for thrombosis.

Knowledge regarding the indicated use of CPA/EE for moderate to severe acne related to androgen sensitivity (with or without seborrhoea) was 92%, and knowledge about the avoidance of its use for contraception alone in women of reproductive age was 81.4%.

Approximately half of physicians (47.7%) were aware of the prescribing for acne only after failure of topical therapy or systemic antibiotics. The percentage of physicians who responded correctly was variable for different contraindications in the product information (59.3%-98.8%). There were some areas with lower levels of knowledge, like hirsutism indication, prescribing after failure of other acne treatments concomitant use with hormonal contraceptives or need to stop treatment with CPA/EE at least 4 weeks prior a major surgery or prolonged immobilisation.

In summary, the knowledge of VTE/ATE risk associated with CPA/EE use was high among prescribing physicians who completed the questionnaire as measured in the PASS. They had a clear understanding of the signs and symptoms of, as well as the risk factors for VTE/ATE. Two additional drug utilization studies performed and currently assessed by PRAC in parallel (as procedures EMEA/H/N/PSR/J/0003vand EMEA/H/N/PSR/J/0005) have further supported these findings.

As alternative ways of increasing physicians' knowledge and understanding of the key information of the educational materials, the PRAC supported the MAH's proposal to liaise with the National Competent Authorities to further explore the feasibility and implementation of alternative communication methods (e.g. using digital media), as applicable, and in accordance with available EU guidance (e.g. addendum to GVP Module XVI). Furthermore publication of the study results in scientific journals by the MAHs is already being pursued and the MAHs are currently exploring with the principal investigators of the three PASS the possibility of extending the communication plans to conferences and journals reaching the audience of potential prescribers.

In conclusion, this report fulfils the study objectives to evaluate physicians' knowledge and understanding of the key safety information in the educational materials regarding CPA/EE.

The benefit-risk balance of the concerned medicinal product(s) remains unchanged.

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

The joint PASS final study report submitted by the MAHs complies with their obligation to perform a PASS to evaluate the effectiveness of the risk minimisation activities 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 PASS final study report, 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 PASS final study report version 1.0 dated 31 May 2016, the PRAC considers that:

☒ the risk-benefit balance of medicinal products containing the active substance cyproterone/ethinylestradiol concerned by the joint PASS 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 PASS final study report are recommended:

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

The MAH(s) should provide a protocol of a PASS within the risk management plan submission, to evaluate the effectiveness of the risk minimisation activities. 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 PASS 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.