Science For A Better Life

Clinical Study Synopsis

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The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

Title	Drug Utilization Study on the Prescribing Indications for CPA/EE[1] in 5 European Countries
Keywords	Diane-35, cyproterone-acetate, ethinyl estradiol, prescribing indications, drug utilization study, DUS, CPA/EE
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. For the treatment of acne, CPA/EE should only be used when alternative treatments, such as topical therapy and systemic antibiotic treatment, have failed. Due to the mode of action, the dosing and the regimen, the preparation also acts as effective contraceptive. In 2012 the French health authority conducted a national review of CPA/EE and highlighted a rare but serious risk of thromboembolic events and off-label use of these medicines as a contraceptive only. This triggered an Urgent Union Procedure at the beginning of 2013. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) concluded that the benefits of CPA/EE combinations (cyproterone acetate 2mg / ethinylestradiol 35mcg) outweigh the risks, providing that several measures are taken to minimize the risk of thromboembolism. These medicines should be used solely for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of reproductive age. Since CPA/EE also acts as a hormonal contraceptive, women should not take these medicines in combination with other hormonal contraceptives. As one of the risk minimization measures, the Marketing Authorization Holders (MAHs) were required to conduct a number of studies including the drug utilization survey described in this final study report.
Research question and objectives	This drug utilization study was designed to compile the reasons and specific indications for the prescription of CPA/EE. The study used a cross-sectional design with a special focus on the clinical decision-making process. The primary objective of the study is to characterize the prescribing behaviors for CPA/EE in 5 European countries (Austria, Czech Republic, France, the Netherlands, and Spain), including: • prescription indications for CPA/EE • use of CPA/EE in accordance with the updated label • concomitant use of CPA/EE and combined hormonal contraceptives (CHCs) • second line treatment of CPA/EE for the indication acne

[1] Cyproterone Acetate and Ethinyl Estradiol

Study Design	This was a multi-national, cross-sectional study. Physicians from the specialties gynecology and dermatology, as well as general practitioners (GPs) were recruited. Each patient who received a CPA/EE prescription during the study period was asked if she was willing to participate. The physicians were requested to provide information on the prescribed CPA/EE drug, the history of CPA/EE prescription for the individual patient, use of concomitant hormonal contraceptives, the patient's androgen-dependent condition(s) characteristics and treatments (including over-the-counter [OTC] medicines), and the reasons for prescribing CPA/EE.
Setting	Physicians were recruited from networks of gynecologists, dermatologists and general practitioners (GPs) in 5 European countries (Austria, Czech Republic, France, The Netherlands and Spain). Because of the very low rate of Dutch physicians willing to participate, additional contact was made in The Netherlands to physicians outside the existing network.
Subjects and Study Size, including dropouts	All women that received a prescription of CPA/EE and consented to participate were eligible for this drug utilization study. The study planned to recruit 1,000 patients per country from a network of 250 physicians (50 per country). Physicians would be a representative sample of those prescribing CPA/EE (i.e. a mix of gynecologists, dermatologists, and GPs). However, the number of physicians willing to participate in the study and the total number of patients receiving CPA/EE was found to be markedly lower than expected, despite various efforts to improve accrual and by prolonging the period of recruitment. A total of 1,513 patients were recruited by 120 physicians.
Variables and Data sources	Recruiting physicians completed a baseline physician questionnaire providing information on the prescriber, including age, gender, specialty, and years of experience. In addition, a baseline questionnaire was completed for each new patient receiving a CPA/EE prescription. Baseline questionnaires were filled in by recruiting physicians and provided details on the following items: • the brand name and the date of the prescribed CPA/EE-containing drug • first use, re-use after a break, or continuous use of CPA/EE • information about androgen-dependent condition(s) (duration, previous and concomitant treatment including OTC medicines and information on treatment failure)

	• reasons for prescribing CPA/EE • concomitant hormonal contraceptive use For reasons of data protection, date-of-birth was obtained from the patient's informed consent form. Data capture was completed using paper questionnaires.
Results	A total of 314 physicians agreed to participate in the study, of which 120 physicians recruited at least one patient. The mean age of the participating physicians was 52.2 years, that of the non-participating physicians 53.1 years. The gender distribution was 57.6% male for participating physicians, vs. 44.9% for the non-participating physicians. The specialties were represented as follows: For those participating, 63.1% gynecologists, 20.1% GPs, 16.9% dermatologists. For the non-participating physicians 36.6% GPs, 31.9% dermatologists, 31.5% gynecologists. In both groups (participating and non-participating) the majority of physicians had 15 or more years of professional experience. Surprisingly, the willingness of physicians to take part in this study was generally very low, particularly in The Netherlands. In France the three-tiered approval process took eight months and was only completed as late as 24th November 2015. As the frequency of prescriptions was lower than anticipated, additional physicians were contacted in all participating countries. Furthermore, the recruitment period was extended in Austria, Czech Republic, The Netherlands and Spain, and continued up until study end in April 2016 instead of the planned date October 2015. Timelines associated with the agreed final report date prevented further recruitment in any of the countries. Due to the late start in France, the French arm of the study is ongoing. However, data that have been obtained in France until the 8th April 2016 were integrated into this report. Overall, the intended number of patients (1,000 patients/county) was not achieved in any of the participating countries. 1,513 patients were recruited at study end. The most frequent indication was acne with 65.6% of the prescriptions (n = 993) followed by. Contraception was mentioned as a reason in 66.7% of all participating patients however the percentage of prescriptions stating contraception only as reason was 16.3%. 2.9% (n = 44) of the enrolled patient used an additional HC. The physicians were able to select multiple reasons for the prescription of CPA/EE. The main reasons for prescription of CPA/EE were contraception (66.7%, n = 1,009) and acne (65.6%, n = 993). The severity distribution of the patients with acne was 36.7% with mild acne, 54.7% with moderate and 8.7% with severe acne. Other androgen-dependent conditions included seborrhea (12.9%), hirsutism

	(12.6%), PCOS (11.4%) and androgenetic alopecia (5.0%). Overall, 83.3% (n = 1,261) of all prescriptions for androgen-dependent conditions. 16.3% of the prescriptions were made due to contraception only, predominantly by GPs and gynecologists. Prescriptions in 522 patients (34.5% of the total study population) reflect an approximation to accordance with the updated label of CPA/EE in the study population of 1513 patients: 301 (19.9%) patients with a diagnosis of moderate to severe acne who had "previous topical and/or systemic antibiotic treatment" and those with hirsutism (14.6%, n = 221). Regarding the previous treatment in the category "moderate to severe acne without hirsutism" (37.3%, n = 564) with topical agents and/or systemic antibiotics (19.9%, n = 301), there seems to be a difference between dermatologists (73.5%) and GPs (77.7%) on the one side, whose patients seem to have been prescribed these modalities more often, and gynecologists (40.1%), whose patients tend to have been prescribed hormonal therapy in the form of CPA/EE more often without such preceding therapy. The prescription of CPA/EE together with another hormonal contraceptive was 2.9% (n = 44). Of those 42 were oral contraceptives and 2 non-oral contraceptives. 35 of the additional HCs were stated by gynecologists. Of 1,028 patients diagnosed with acne, 586 (57.0%) received previous treatment. In 428 (41.6%) the treatment was reported to have failed. 564 (54.9%) patients in the category "moderate to severe acne without hirsutism". Of these, 301 (29.3%) received previous topical treatment and/or systemic antibiotics, which had failed in 249 (24.2%) cases.
Discussion	Most prescriptions of CPA/EE were indicated for the treatment of androgen-dependent conditions. Prominent among these conditions was acne, which was mentioned in two thirds of all prescriptions. When acne, seborrhea, hirsutism, polycystic ovaries and androgenetic alopecia are included, alone or in combination, 83.1 % of prescriptions were related to androgenic pathology. Prescriptions exclusively for indications not related to an androgen-dependent conditions (contraception only) constitute 16.3% or approximately one sixth of all prescription events. The severity of acne is described as moderate to severe in almost two thirds (63.1%) of the prescriptions. The documentation of preceding treatments with other topical agents or systemic therapeutics is likely to be incomplete because of the more intense work needed to fill out the details, including preparations and dates of treatment. Additionally, patient initiated skin-care with OTC and cosmeceuticals is probably subject to recall bias. Therefore, this information may represent the prescribing behavior to a lesser extent than the documentation of acne itself. The prescription of CPA/EE together with another hormonal contraceptive is less than 3%. The

	study indicates a strong relationship between the prescription of CPA/EE and disorders with a pathophysiology associated with an androgen excess. For the 16.3% of cases where CPA/EE is prescribed as a contraceptive without documentation of any such disorder, the motives for the choice of this particular combination cannot be clarified by this study.
Marketing Authorisation Holder(s)	Bayer HealthCare Pharmaceuticals Müllerstraße 178 13353 Berlin Germany
Names and affiliations of principal investigators	Principal Investigator Klaas Heinemann, MD, PhD, MSc, MBA ZEG – Berlin Center for Epidemiology and Health Research Invalidenstrasse 115 10115 Berlin Germany