Annex II

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

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

The CMDh, having considered the PRAC recommendation dated 16 May 2013 with regards to the cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products, agrees with the recommendation therein as stated below:

Overall summary of the scientific evaluation of cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal product(s) by PRAC

In January 2013 the French medicines agency (ANSM) took the decision to suspend cyproterone acetate/ethinylestradiol (CPA/EE) (2mg/0.035mg) containing medicinal products in France within three months. ANSM considered the risk of venous and arterial thromboembolism (VTE and ATE) to outweigh the benefits in treating acne.

In view of the above, on 4 February 2013 France requested the PRAC under Article 107i of Directive 2001/83/EC[1] to assess the above concerns regarding thromboembolism and its impact on the benefit-risk balance for cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) containing medicinal products, and to give its opinion on measures necessary to ensure the safe and effective use, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

Cyproterone acetate exerts its anti-androgenic effect by blocking androgen receptors. It also reduces androgen synthesis by a negative feedback effect on the hypothalamo-pituitary-ovarian axis.

The product was authorised firstly in Germany in 1985 and followed the rest of the EU countries. The wording of the indication of cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products varies between the EU Member States. In general, cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products are authorised for treatment of androgenic symptoms in women, such as pronounced forms of acne, seborrhoea, and mild forms of hirsutism. In some Member States is also authorised for alopecia androgenetica.

The combination of cyproterone acetate/ ethinylestradiol (2mg/0.035mg) acts simultaneously as a hormonal contraceptive.

Cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products are known to increase risk of thromboembolic events (TE). In July 2002, the Pharmacovigilance Working Party (PhVWP) discussed the increased venous thromboembolic (VTE) and arterial thromboembolic (ATE) risks and concluded that the use of cyproterone acetate/ethinylestradiol (2mg/0.035mg) should be restricted taking into account the thromboembolic events. The wording agreed by the PhVWP is entirely implemented only in 11 Member States.

Thromboembolic events are adverse events which usually occur in a vein of the leg (deep vein thrombosis). When diagnosis is not made and no treatment is started, or when the thrombosis does not give any clear symptoms, the clot can move upwards to the lung (pulmonary embolism) or the brain (cerebral embolism). Misdiagnosis is a realistic possibility since TE has diffuse symptoms and is a rare event in population of healthy young women. Overall, VTE could be fatal in 1-2% of the cases.

Known risk factors for VTE include history of VTE, pregnancy, trauma, surgery, immobilisation (e.g. after surgery or long flights), obesity and smoking (i.e. all situations of a prothrombotic state). Also there are certain hereditary thrombophilic defects that increase the risk. Checking personal and family

[1] French assessment report February 2013 Rationale for the triggering of procedure under Article 107i of Directive 2001/83/EC on cyproterone/ethinylestradiol (2mg/0.035mg) presented by ANSM, France

history of VTE before prescribing EE-containing medicinal products (e.g. combined oral contraceptives (COC)) is, therefore, recommended in the product information of the products.

It has been shown that risk of VTE is highest during the first year a woman starts hormonal contraceptives or when she re-starts after a period of non-use of at least one month (Dinger *et al,*. 2007). After an initially higher risk (the first year), the risk drops to a constant lower level.

For the treatment of acne, topical therapies are applied for mild to moderate acne without hyperandrogenic state. They include benzoylperoxide, retinoids, antibiotics, salicylic acid, and azelaic acid. Alternative treatments for moderate to severe acne are long-term antibiotics (topical or systemic), keratolytics and retinoids (topical or systemic, with known risks of teratogenicity and subject to a pregnancy prevention plan and regular liver function testing). In addition, there are other known alternative pharmacological treatments for severe androgenic symptoms (especially hirsutism).

Clinical safety

The PRAC reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience on the safety of cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products, as well as stakeholders' submissions in particular with regards to the thromboembolic events.

a. Thromboembolic events

Clinical studies

To assess venous and arterial thromboembolic effects from clinical studies with CPA/EE, only clinical studies that documented adverse events are discussed here.

The MAH- of the originator product sponsored 10 phase-III clinical trials providing information on safety of these medicinal products. The total number of patients exposed in these studies amounts to 2455.

With exception of study report AI58, no cases of VTEs or ATEs were reported in patients from the 10 MAH- sponsored clinical trials with ~~(~~CPA/EE~~)~~ (2mg/0.035mg). In study AI58, one patient on CPA/EE developed VTE.

The MAH conducted a systematic review of the scientific literature (cut-off date: 14 Feb 2013) in MEDLINE, EMBASE, Derwent Drug File, and BIOSIS Previews on clinical studies covering cardiovascular diseases and CPA/EE(2mg/0.035mg). In none of the 118 identified clinical studies described in the scientific literature a venous or arterial thromboembolic/cardiovascular event during course of the study was reported.

Post-marketing safety surveillance studies

There are two large, ongoing post-marketing surveillance studies which yield incidental data on the use of CPA/EE (2mg/0.035mg) containing medicinal products. These studies (INAS-OC and INAS-SCORE) investigate the safety of the combined oral contraceptive drugs YAZ (3 mg drospirenone/0.020mg ethinylestradiol) and Qlaira (dienogest/estradiol valerate, step down dose regimen) respectively. Hormone preparations containing CPA/EE (2mg/0.035mg) are part of the comparator arms in these studies. In both studies all enrolled women receiving a prescription for an oral contraceptive were questioned about the reason for the prescription at baseline (after having received the prescription). Due to the observational nature of these two studies comparing newly marketed combined oral contraceptives with a comparator group there was no restriction of the comparator group to specific oral hormonal combinations. Healthcare professionals enrolled CPA/EE (2mg/0.035mg) users into the

studies due to the fact that in many European countries CPA/EE (2mg/0.035mg) mentions contraception in women requiring treatment for androgen dependent skin conditions.

INAS-OC

INAS-OC is a prospective, non-interventional, active surveillance study designed to assess the risk of short- and long-term use of YAZ (3 mg drospirenone/0.020mg ethinylestradiol), Yasmin (3 mg drospirenone/0.030mg ethinylestradiol) and of oral contraceptives and CPA/EE (2mg/0.035mg), conducted in 6 European countries and United States. The primary outcomes of interest are cardiovascular events, in particular the incidence of VTE and ATE, during oral contraception use. A total of 1672 users of CPA/EE (2mg/0.035mg) -containing preparations were enrolled in the study representing 7.5% of the total study population.

In this study, around 60% of women prescribed a CPA/EE-containing preparation specifically reported in the baseline questionnaire that their CPA/EE (2mg/0.035mg) prescription was due to acne and/or polycystic ovary syndrome (PCOS). This is despite the fact that the study enrolment criteria overwhelmingly selected for patients in whom contraception would have been the original reason for consultation. The fact that the women recalled the link with acne / PCOS indicates that the need for treatment of the skin condition / hyperandrogenism of the individual woman was specifically discussed during the visit and drove the prescription of CPA/EE (2mg/0.035mg).

INAS-SCORE

INAS-SCORE was initiated after the launch of Qlaira (dienogest/estradiol valerate, step down dose regimen) in Europe (September 2009) and USA (October 2010) and is a prospective non-interventional post-approval safety study conducted in Austria, France, Germany, Italy, Poland, Sweden, UK and the US. The study (currently ongoing) seeks to assess the risks of short- and long-term use of Qlaira (dienogest/estradiol valerate, step down dose regimen) and of oral contraceptives and including CPA/EE (2mg/0.035mg).

A total of 1094 users of CPA-containing preparations were enrolled in the study, representing 5.5% of the total study population based on 6th Interim Report of this on-going study.

In this study almost 67% of women prescribed CPA-containing preparations remembered after the discussion with their healthcare professional that their individual prescription was written for acne and/or PCOS, indicating that the skin condition was discussed during the counselling and was mentioned as the main reason to prescribe CPA/EE (2mg/0.035mg).

The MAH commented that data from these two studies indicate that, even where the primary reason for consultation is almost certainly contraception, 63% of prescriptions for CPA/EE (2mg/0.035mg) could be linked by the patients themselves to acne and/or other hyperandrogenous conditions. Direct questioning of the prescribing physician would be needed to ascertain this true proportion. No study collected such data and therefore this design limitation must be kept in mind when interpreting the data.

Cohort studies

The MAH provided an overview of 6 cohort studies (of which 2 with additional nested case-control analyses) and 7 case-control studies assessing the VTE risk associated with CPA/EE and one cohort study assessing the ATE risk associated with CPA/EE. In these studies VTE risk among CPA/EE users was compared to the VTE risk of non-use as well as of various types of combined oral contraceptives (COCs). No comparative safety data vs products that are registered for the treatment for acne/hirsutism/PCOS are presented.

None of the studies presents information on the fatality rate of VTE among CPA/EE users, except for the Seaman 2003 study stating that none of the 179 VTE events, including the 23 events among CPA/EE (2mg/0.035mg) exposed, was fatal.

Several observational studies have assessed the VTE risk with use of CPA/EE (2mg/0.035mg). Studies show considerable variability in their relative risk compared to non-use or other COCs and in their absolute risk for VTE. Early studies reported that the risk of (idiopathic) VTE in users of CPA/EE is greater in comparison to users of levonorgestrel-containing COC, or conventional COC respectively, with low estrogen (<50µg) (Vasilakis-Scaramozza & Jick 2001, Seaman *et al*, 2003). Subsequent studies (Lidegaard *et al.* 2003, Seaman *et al*. 2004), the latter addressing the issue of confounding, concluded that the absolute risk of VTE among women taking CPA/EE is not significantly greater than for women on COCs. More recent studies assessing the VTE risk in users of various COCs and CPA/EE (including Lidegaard 2009, Hylckama 2009) had major methodological flaws (missing data for confounders) that raise questions about the validity of their conclusions. In addition, usage patterns of CPA/EE and COCs for oral contraception may differ significantly.

Interruption and restarting is likely to be more frequent for CPA/EE (2mg/0.035mg) which is indicated for treatment of androgen-dependent diseases such as acne, and for which the product label implies that the medication may be discontinued after improvement of symptoms and be restarted in case of recurrence of symptoms. As recent data have demonstrated, restarting or switching COC use after interruption is associated with an excess risk. Overall, there is no conclusive evidence for a higher VTE risk with CPA/EE (2mg/0.035mg) compared to COCs, including those containing levonogestrel.

Epidemiological studies have suggested an association between the use of COCs in general and an increased risk of arterial thrombotic and thromboembolic diseases such as myocardial infarction, and of cerebrovascular accidents. These events occur rarely. Arterial thromboembolic events may be life-threatening or may have a fatal outcome. There is only sparse data on arterial thrombotic and thromboembolic diseases with CPA/EE (2mg/0.035mg) or cyproterone acetate alone. In a recent study (Lidegaard, 2012) the comparative analyses of the relative risk for thrombotic stroke and myocardial infarction between the various progestins, including levonorgestrel, and non-use are in the same magnitude and do not show differences between the various progestins. In addition, with regard to CPA/EE (2mg/0.035mg) vs. non-use statistical significance is even not achieved.

Post-marketing reporting

Thromboembolic events are known, rare adverse drug reactions associated with the use of estrogen-progestogen containing preparations including CPA/EE (2mg/0.035mg).

The MAH of the originator has submitted in the annual Periodic Safety Update Reports (PSURs) for CPA/EE information on thromboembolic events. As of last PSUR (reporting period 01 Jun 2011 – 31 May 2012, DLP: 31 May 2012), the reporting frequency of all (arterial, venous and unspecified) thrombotic / thromboembolic events received during the reporting period was 1.3 per 100,000 women-years. Compared with a corresponding reporting frequency ranging between 0.8 and 1.5 per 100,000 women-years during the previous six PSUR periods, there is no evidence of an overall increased reporting frequency of thrombotic /thromboembolic events. The reporting frequency is less than the incidence of VTE as reported in epidemiological studies.

For the period since the global launch of CPA/EE (2mg/0.035mg) through 30 Jan 2013, 968 cases (serious (93%) and non-serious (7%), medically confirmed (85%) and non-medically confirmed (15%) reporting thrombotic/thromboembolic events irrespective of their nature (arterial, venous and unspecified) occurring in female patients were received by the MAH from worldwide sources. One of these 968 cases was reported from clinical trial ME94162 / AI58. These 968 cases comprise 7% of the total number of ADR reports received cumulatively through 30 Jan 2013 (n = 13,875 in total).

CPA/EE (2mg/0.035mg) was prescribed according to the indication (i.e. androgenic symptoms) in 40% of cases and prescribed off-label in 31% (as a contraceptive or for menstrual irregularities). In 30% of cases the indication for prescription was unknown.

The overall global spontaneous reporting rate for all cases reporting any thrombotic /thromboembolic event is 1.3 per 100,000 women-years. The estimate is based on the calculated global patient exposure of 75,417,345 women-years and 968 received TE reports worldwide.

Age was reported for 877 of 968 (90.6%) patients. Patients were between 13 and 63 years old (mean 27 years, median 25 years) at the time of the event. 88 (9.1%) ADR reports referred to patients less than 18 years of age, 639 (66%) patients were between 18 and 35 years of age and 150 (15.5%) reports referred to patients older than 35 years of age. No age was reported for 91 (9.4%) patients.

Weight and height were reported for 258 (26.7%) of 968 patients. BMI for these patients was between 15 and 54 (mean 24, median 23), whereas BMI over 30 kg/m^2 was documented in 33 (3.4%) of these reports.

Most reports were from patients between 18-35 years of age (66%). This does not indicate a higher incidence in this age group but only a higher reporting rate in this age group, as patient exposure has not been provided in age categories.

Concomitant medications

For 879 (90.8%) of 968 TE cases, CPA/EE (2mg/0.035mg) was the only suspected drug. CPA/EE (2mg/0.035mg) is often used in combination with cyproterone 10 mg (CPA 10 mg) in different daily doses to increase anti-androgenic effects. Therefore retrieved cases of reporting TE adverse reactions from worldwide sources comprise also cases occurring in association with CPA/EE (2mg/0.035mg) in combination with CPA 10 mg (n = 48 [5%] cases in total). The combined therapy with CPA/EE and CPA 10 mg has a different safety profile as reflected in the labelling of CPA 10 mg.

Furthermore, concomitant use of another hormonal contraceptive being reported as an additional suspected drug was documented in 21 (2.2%) of received TE cases; 20 patients received concomitantly various COCs and one case reported concomitant intrauterine device (IUD) (levonorgestrel-releasing intrauterine system) use.

In addition, co-suspected drugs, such as citalopram, thalidomide, olanzapine, antineoplastic agents, natalizumab, methylprednisolone sodium succinate, antibiotics or isotretinoin were reported for 20 (2.1%) patients.

Non-fatal cases

892 (92.1%) of 968 cases reported non-fatal TE in association with CPA/EE (2mg/0.035mg) use, of which 760 were medically confirmed. This translates into a global spontaneous reporting rate of 1.2 non-fatal TE reports per 100,000 women-years with CPA/EE (2mg/0.035mg).

Fatal cases

In total, 76 (7.9%) of 968 ADR reports with TE events reported fatal outcomes; 66 were medically confirmed and 10 were non-medically confirmed consumer reports.

This translates into the global spontaneous reporting rate of 0.10 fatal TE reports per 100,000 women-years with CPA/EE (2mg/0.035mg). Of these 76 reports, 67 (88.2%) cases reported pulmonary embolism with or without reported DVT or unspecified thrombosis, 8 (10.5%) reports described cerebral events, and 1 (1.3%) reported events of dyspnoea, disseminated intravascular coagulation and circulatory disorder in context of multi-organ failure, acute hepatic failure, coma hepatic, bone marrow failure, fungal sepsis, pneumonia and histiocytosis haematophagic in a female patient with

condition of alcohol abuse, acute myeloid leukaemia, polychemotherapy and antibiotics therapy. There were no cases reporting ATE with a fatal outcome.

Arterial thromboembolic events

A total of 52 (5.4%) of 968 retrieved cases reported one or more ATEs in association with CPA/EE (2mg/0.035mg) use.

This translates into reporting rate of 0.07 ADR reports per 100,000 women-years with CPA/EE (2mg/0.035mg). The estimate is based on the calculated patient exposure of 75,417,345 women-years and 52 reports of arterial embolic and thrombotic events worldwide.

There were no cases reporting ATE with a fatal outcome.

Venous thromboembolic events

A total of 789 (81.5%) of 968 retrieved cases reported one or more VTEs in association with CPA/EE (2mg/0.035mg) use.

This translates into reporting rate of 1.05 ADR reports per 100,000 women-years with CPA/EE (2mg/0.035mg). The estimate is based on the calculated patient exposure of 75,417,345 women-years and 789 reports of venous embolic and thrombotic events worldwide.

Information received after cut-off date 30 January 2013

Following the media attention after the initiation of the referral procedure a number of reports were submitted reciprocally. A total of 175 cases (all serious, medically confirmed (38.3%, n=67 in total) and non-medically confirmed (61.7%, n=108 in total)) reporting thrombotic / thromboembolic events (TE) irrespective of their nature (arterial, venous and unspecified) occurring in female patients in association with CPA/EE (2mg/0.035mg) were received by the MAH from worldwide sources additionally to the 968 TE cases presented in the main analysis. Of these 175 cases, 15 reported fatal outcome (4 medically confirmed and 11 non-medically confirmed consumer reports).

The updated total number of cases through 6 Mar 2013 amounts to 1143 reports with TE.

The overall global spontaneous reporting rate for all cases reporting any TE event at data lock point (DLP) 06 Mar 2013 is estimated as 1.5 per 100,000 women-years, 1.4 non-fatal TE reports per 100,000 women-years, and 0.1 fatal TE reports per 100,000 women-years with CPA/EE (91 fatal cases (8%) in total of 1143 cases).

In conclusion, the thromboembolic events are known adverse drug reactions associated with the use of estrogen-progestogen containing preparations. An increased risk for thrombotic / thromboembolic events (that may be fatal in 1-2% of cases) is listed in the Core company data sheet (CCDS) for CPA/EE (2mg/0.035mg).

In addition information in the section on circulatory disorders on the switch or restart was recommended by PRAC. More specifically the excess risk of VTE is highest during the first year a woman starts CPA/EE (2mg/0.035mg) or when restarting or switching after a pill-free interval of at least a month.

b. Off Label Use

The off-label use was defined according to the therapeutic indications for CPA/EE (2mg/0.035mg) as SmPC indication statements differ from country to country on the basis of national responses of health authorities to the EMA Pharmacovigilance Working Party (PhVWP) review of the product conducted in 2002.

Off-label use would primarily equate to prescription of CPA/EE (2mg/0.035mg) as a contraceptive in patients with no requirement for acne treatment. Several databases were consulted.

The IMS prescription data have limited value because they do not include a category of "contraception in the absence of acne". Furthermore, the data do not systematically provide information on the medical history of the patient (e.g. history of acne or hyperandrogenic symptoms) or clinical findings as doctors tend to fill out the minimum mandatory information for the IMS. This missing information would be essential to assess the true motives of the prescribers in choosing one product over another.

Cegedim Promotional data show 32% of use in contraception only, while Longitudinal data show 3.4% use in contraception only; the Pharmalink Panel data for Germany show 53% of contraceptive use, of which 75% the reason given is for acne and 25% for other reasons.

It has to be noted that Polycystic ovarian syndrome (PCOS) mentioned by HCPs as an indication reflects the use of CPA/EE for the treatment of androgen related symptoms of PCOS such as acne or hirsutism.

The IMS Prescriptions Insight Data for France (ANSM benefit/risk review, 5 Feb 2013) suggest that CPA/EE (2mg/0.035mg) containing medicines are prescribed for contraception.

This is the case in 54% of the 60% of prescriptions written by general practitioners (i.e. 32.4% of all prescriptions) and in 75% of the 36% of prescriptions written by gynaecologists (27.8% of all prescriptions), which implies that around 60% of all French prescriptions for CPA/EE (2mg/0.035mg) relate to contraception and therefore would be off-label use taking into account the indication only in acne in France.

Two large, ongoing post-marketing surveillance studies (INAS-OC and INAS-SCORE) yield incidental data on the use of CPA/EE. These studies investigate the safety of the combined oral contraceptives YAZ (3 mg drospirenone/0.020mg ethinylestradiol) and Qlaira (dienogest/estradiol valerate, step down dose regimen) respectively. Hormone preparations containing CPA/EE were part of the comparator arms in these studies.

These studies give some information regarding the use of CPA/EE (2mg/0.035mg) as a contraceptive.

In INAS-OC study 28.1% of use is in contraception, from a total of 1672 users of CPA-containing preparations enrolled in the study, representing 7.5% of the total study population. In this study, around 60% of women prescribed a CPA-containing preparation specifically reported in the baseline questionnaire that their CPA/EE (2mg/0.035mg) prescription was due to acne and/or PCOS.

In the INAS-SCORE study 20.2% of use is in contraception from a total of 1094 users of CPA-containing preparations which represents 5.5% of the total study population.

Data from these two studies indicate that, even where the primary reason for consultation is almost certainly contraception, 63% of prescriptions for CPA/EE (2mg/0.035mg) could be linked by the patients themselves to acne and/or other hyper-androgenous conditions.

It is evident that in the current approved indications in EU, off-label use is observed. According to the 2012 IMS data issued from 16 European countries, the percentage of CPA/EE (2mg/0.035mg) prescription in acne varies from 0 to 54% with a median at 9%. The PRAC considered all the above data for the CPA/EE (2mg/0.035mg) containing medicinal products and recommended clarification on the indication of the products.

Conclusions on safety

In conclusion the PRAC considered all currently available safety data for the CPA/EE (2mg/0.035mg) containing medicinal products and recommended that these products should be contraindicated in patients with history or hereditary predisposition of venous thrombosis. In addition the PRAC stressed that these products should not be given concomitantly with other hormonal contraceptives and also that the need to continue treatment should be evaluated periodically knowing that the time to relief of symptoms is at least three months.

Clinical efficacy

CPA/EE (2mg/0.035mg) containing medicinal products have anti-androgenic effects. The effects on hirsutism and seborrhoea have mainly been studied in the context of treatment of acne and/or polycystic ovary syndrome (PCOS).

In women with androgenic sensitive skin conditions, the efficacy in moderate and severe acne with/without seborrhoea and/or hirsutism is demonstrated in more than 30 sponsored and non-sponsored trials, including comparative trials, uncontrolled trials, and pilot studies. The time to relief of symptoms is at least three months and the effects are more pronounced with longer treatment duration.

a. Treatment of hirsutism

For the treatment of hirsutism alone (mostly in PCOS patients), 13 studies demonstrated efficacy versus other treatments. A recent published study comparing CPA/EE (2mg/0.035mg) and drospirenone/EE, and desogestrel/EE showed that after 6 months these medicinal products were equally efficacious but after 12 months CPA/EE (2mg/0.035mg) showed the strongest anti-androgenic effect, followed by drospirenone/EE, and desogestrel/EE as the weakest. This is expected in view of the differences in anti-androgenic properties of cyproterone, drospirenone and desogestrel. Cyproterone has the strongest anti-androgen activity.

In the Cochrane review on treatment of hirsutism nine clinical studies qualified for inclusion. Only one study evaluated the efficacy of CPA/EE (2mg/0.035mg) versus placebo. In that study there was a significant subjective improvement in hirsutism, however no objective evaluation was performed.

In comparison with other medical treatment options, no clinical differences in hirsutism were detected when CPA/EE (2mg/0.035mg) was compared to other medicinal products (spironolactone, finasteride, GnRH analogues, ketoconazole). The only difference in clinical outcome was a significantly improved Ferriman Gallwey (FG) score at 12 months when cyproterone acetate was compared with flutamide.

b. Seborrhoea

Seborrhoea has mainly been evaluated in the context of acne. The effect of CPA/EE (2mg/0.035mg) on seborrhoeic symptoms, such as greasy skin and hair, starts after 3-4 cycles of treatment, and results are more pronounced with longer treatment. Similar to acne treatment, percentages of improvement vary per study, and depend on the methods applied for evaluation of effects.

c. Alopecia androgenetica

The data on efficacy of CPA/EE in alopecia androgenetica, except for the mechanism of action, is limited to one small study (DeCecco L *et al,* 1987) in which some limited beneficial effects were noted.

d. Acne without androgenic features

Regarding acne without androgenic features, one study compared CPA/EE with systemic antibiotic tetracycline and showed similar efficacy (Greenwood R, *et al.,* 1985). Two studies (A18566, 2004,

Palombo-Kinne E, *et al.,* 2009) comparing CPA/EE (2mg/0.035mg) with dienogest containing combined oral contraceptive and with norgestimate containing combined oral contraceptive also showed similar efficacy.

Two studies compared CPA/EE (2mg/0.035mg) with levonorgestrel/EE (LNG/EE). Results indicated that after 6 month treatment the efficacy of CPA/EE (2mg/0.035mg) was superior and statistically significantly better than for LNG/EE.

The recent Cochrane review (Arowojolu, AO. *et al.*, 2012), which evaluated efficacy of combined oral contraceptives in acne, reported that regarding the differences in the comparative effectiveness of the contraceptives, data were too limited for any conclusive comparison. However, based on the best evidence available, the authors concluded that the treatment containing cyproterone acetate improved acne better than a levonorgestrel-containing treatment; that treatment with cyproterone acetate showed better acne outcomes than one with desogestrel, but the studies produced conflicting results; and finally that drospirenone-containing treatment appeared to be more effective than norgestimate or nomegestrol acetate-containing treatment but less effective than treatment with cyproterone acetate.

e. Contraceptive effect

The contraceptive effect of CPA/EE (2mg/0.035mg) was investigated in several studies at the time of authorisation. The overall Pearl Index for CPA/EE (2mg/0.035mg) in a large clinical trial was 0.12 with an upper 95%-confidence limit of 0.44. The calculations met the precision requirements of the Guideline on clinical investigation of steroid contraceptives in women[2].

Table 1 Pearl Index based on CPA/EE (2mg/0.035mg) clinical trial data (Study 8186, Aydinlik *et al.,* 1990)

	Method failure	Total
number of cycles	20,746*	21,196
number of pregnancies	0	2
Pearl Index	0	0.1226647
two-sided 95% confidence interval	0; 0.2311345	0.01485552; 0.4430523

*calculated as the total number of cycles, n=21,196, minus the number of cycles, n=450, in which medication was missed.

In addition the contraceptive effect of CPA/EE (2mg/0.035mg) was investigated in a European Active Surveillance (EURAS) study. The comparison of Pearl Indices in the EURAS study demonstrated the Pearl Index of CPA/EE (2mg/0.035mg) to be 0.37 (95% CI 0.19-0.65), which is comparable with that obtained for approved combined contraceptives (which vary between 0.48 and 0.63).

Conclusions on efficacy

The PRAC considered all the cumulative efficacy and safety data submitted for the indications of acne and seborrhea, hirsutism and alopecia. It also noted the available data concerning the hormonal contraceptive effect of CPA/EE (2mg/0.035mg) containing medicinal products. The PRAC is of the opinion that the benefits of CPA/EE (2mg/0.035mg) containing medicinal products continue to outweigh the risks in the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age. For the treatment of acne, the medicinal products should only be used after topical therapy or systemic antibiotic treatments have failed. For the condition of alopecia in view of the very limited efficacy data, the PRAC concluded that the benefit-risk balance is not favourable and therefore these medicinal products should no longer be indicated in this therapeutic indication.

[2] Guideline on clinical investigation of steroid contraceptives in women. EMEA/CPMP/EWP/519/98 Rev 1., (2005)

Risk minimisation measures

As part of the risk minimisation measures the PRAC adopted an updated indication taking all the data into account, and making clear the conditions for which these products are indicated.

In view of the risks of VTE and ATE the PRAC considered there was a need to ensure that all relevant information for the safe use of these products should be applied across authorised products and therefore agreed on the wording for all relevant sections dealing with the risk of VTE/ATE.

The PRAC endorsed a Direct Healthcare Professional Communication (DHPC), to communicate the outcome of the present review and to communicate to the healthcare professionals the updated indication and to highlight the risk of the thromboembolic events.

The PRAC also agreed on the need of a risk management plan to be submitted as these medicinal products do not have an EU risk management plan in place.

In addition the PRAC requested a study protocol to be provided within the risk management plan submission, for a drug utilisation study in order to better characterise prescribing practices for these medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription.

Furthermore the PRAC requested that the protocol of a PASS should be submitted within the risk management plan submission, to evaluate the effectiveness of the risk minimization activities.

Finally educational material for prescribers on the risk of VTEs and ATEs as well for patients for awareness of the VTEs and ATEs symptoms have been requested by PRAC for submission within the risk management plan. This was also one of the main points that the expert group meeting recommended to PRAC.

Benefit-risk balance

The PRAC concluded that the benefit-risk balance of cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products is favourable as the benefits continue to outweigh the risks in the 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, the medicinal products should only be used after topical therapy or systemic antibiotic treatments have failed. In addition the PRAC noted that these medicinal products have hormonal contraceptive effects and as such the concomitant use with another hormonal contraceptive is contraindicated. Furthermore PRAC agreed on other changes to the product information, additional pharmacovigilance activities and risk minimisation measures to address the risk of thromboembolic events. For the condition of alopecia in view of the overall available safety data, in particular in relation to the risk of serious thromboembolic events, and very limited efficacy data, the PRAC concluded that the benefit-risk balance is not favourable and therefore these medicinal products should no longer be indicated in this therapeutic indication.

Overall conclusion and conditions to the Marketing Authorisations

The PRAC, having considered the matter as set out in the appended referral assessment report recommends that

a. the marketing authorisation holders should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study;

b. the marketing authorisation holders should implement risk minimisation measures;

c. the marketing authorisations should be varied.

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate the outcome of the present review.

The PRAC also recommended that the MAH should submit a full risk management plan (RMP) within 3 months following the decision of this procedure. The protocol of drug utilisation study in order to better characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription should be also be submitted as part of the RMP.

The PRAC concluded that the risk-benefit balance of cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal product(s) in the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age remains favourable subject to the restrictions, warnings, other changes to the product information, additional pharmacovigilance activities and additional risk minimisation measures agreed.

Grounds for PRAC recommendation

Whereas

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC, for cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products.
- The PRAC reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience on the safety of cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products, as well as stakeholders' submissions in particular with regards to the risk of thromboembolic events.
- The PRAC confirmed the known risk of thromboembolism of cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products, and recommended clear labelling of symptoms of thromboembolic events, as well as the risk factors for thromboembolic events.
- The PRAC also considered all the cumulative efficacy and safety data submitted for the indications of acne and seborrhea, hirsutism and alopecia.
- The PRAC also noted the available data concerning the hormonal contraceptive effect of cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products.
- The PRAC is of the opinion that the benefits of cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products continue to outweigh the risks in the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhea) and/or hirsutism, in women of reproductive age. For the treatment of acne, the medicinal products should only be used after topical therapy or systemic antibiotic treatments have failed.
- The PRAC also considered that in view of the currently available safety data in order to maintain a favourable benefit/risk for the indications referred above cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products should be contraindicated in patients with history or hereditary predisposition of venous thrombosis. In addition the PRAC stressed that these products should not be given concomitantly with other hormonal contraceptives. The PRAC also recommended further changes to the product information including that the need to continue treatment should be evaluated periodically knowing that the time to relief of symptoms is at least three months.
- The PRAC also concluded that there was need for further risk minimisation measures such as information to patients and healthcare professionals. A drug utilisation study to characterise

prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers was also considered. Furthermore the PRAC requested that a PASS will be conducted to evaluate the effectiveness of the risk minimisation activities.

- For the condition of alopecia in view of the overall available safety data, in particular in relation to the risk of serious thromboembolic events, and very limited efficacy data, the PRAC concluded in accordance with Article 116 of Directive 2001/83/EC that the risk-benefit balance is not favourable and therefore these medicinal products should no longer be indicated in this therapeutic indication.

The PRAC in accordance with Article 107j(3) of Directive 2001/83/EC, recommended by majority that

a. the marketing authorisation holders should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study, as well as a drug utilisation study (see Annex IV – Conditions of marketing Authorisations);

b. the marketing authorisation holders should implement risk minimisation measures;

c. the marketing authorisations of the cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products (see Annex I) should be varied (in accordance with changes to the product information as set out in Annex III).

CMDh position

The CMDh having considered the PRAC recommendation dated 16 May 2013 pursuant to Article 107k(1) and (2) of Directive 2001/83/EC reached a position on the variation to the terms of the marketing authorisations of cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products for which the relevant sections of the summary of product characteristics and package leaflet are set out in Annex III and subject to the conditions set out in Annex IV.