EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 May 2013
EMA/339116/2013

Assessment report cyproterone acetate/ethinylestradiol (2 mg/0.035 mg) containing medicinal products

Procedure under Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1357

Assessment Report as adopted by the PRAC with all information of a confidential nature deleted.

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1. Background information on the procedure

Cyproterone acetate / ethinylestradiol (CPA/EE) (2mg/0.035mg) is a medicinal product for treatment of androgen-dependent symptoms in women. Marketing authorisation for the innovator product was first granted in Germany in October 1985. Currently, cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products have a marketing authorisation in 135 countries and are marketed in 116 countries.

In January 2013 the French medicines agency (ANSM) took the decision to suspend cyproterone acetate/ethinylestradiol (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effective use, and on whether the marketing authorisation for this product should be maintained, varied, suspended or withdrawn.

2. Scientific discussion

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 exact 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) is considered a treatment of androgenic symptoms in women, such as pronounced forms of acne, seborrhoea, and mild forms of hirsuitism. It may also have limited effects on alopecia androgenetica.

Because of its hormonal composition (additional ethinylestradiol component), CPA/EE (2mg/0.035mg) containing medicinal products act simultaneously as contraceptives. Like other ethinylestradiol containing medicinal products, 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 VTE/ATE risk and concluded that the use of CPA/EE (2mg/0.035mg) should be updated regarding the thromboembolic events. The PhVWP wording is entirely incorporated only in 11 member states.

Thromboembolic events

Thromboembolic events are rare 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 vein thrombosis does not give any clear symptoms, the clot can move upwards to the lung (pulmonary 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[2].

Known risk factors for VTE include history of VTE, pregnancy, trauma, surgery, immobilization (e.g. after surgery or long flights), obesity, and smoking (i.e. all situations of a prothrombotic state). Also

[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

[2] CHMP public assessment report combined oral contraceptives and venous thromboembolism. EMEA/CPMP/2201/01/en/final (2001)

there are certain hereditary thrombophilic defects that increase the risk. [3, 4] Checking personal and family history of VTE before prescribing EE-containing medicinal products (e.g. combined oral contraceptives (COC)) is, therefore, recommended.

It has been shown that risk of VTE is highest during the first year a woman starts COCs [2,5] or when she restarts after a period of non-use of at least 1 month.[6] After an initially higher risk (the first year), the risk drops to a constant lower level.

Current alternative treatments

Topical therapies are applied for mild to moderate acne without hyperandrogenic state. They include benzoylperoxide, retinoids, antibiotics, salicylic acid, and azelaic acid. Treatment with combined hormonal contraceptives is also proposed.

Alternative treatments for (serious) acne are long-term antibiotics (topical or systemic, with risk of resistance and in some cases teratogenicity), keratolytics, and retinoids (topical or systemic, with risk of teratogenicity). The systemic form of isotretinoin may only be prescribed by dermatologists as a second line of treatment. It is hepatotoxic and teratogenic, therefore is subject to a pregnancy prevention plan and regular liver function testing.

For the specific combination of symptoms of acne and especially hirsutism in the context of androgen sensitivity, only one licensed alternative therapy is available, i.e. monotherapy with cyproterone acetate (Androcur 10, 50, and 100 mg). However, CPA monotherapy (exposing the patient to a higher dose of CPA) should be combined with adequate hormonal contraception because of foetotoxic effects and could therefore not be used as monotherapy.

In addition, there are experimental pharmacological treatments for severe androgenic symptoms (especially hirsutism), such as spironolactone, gonadotropin-releasing hormone- (GnRH-) agonists, ketoconazole, metformin, and pioglitazone.

2.1. Clinical aspects

2.1.1. 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.

Thromboembolic events

Clinical studies

To assess venous and thromboembolic effects from clinical studies with cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products only clinical studies that documented relevant adverse events were considered.

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3 van Vlijmen EFW *et al.,* (2007). Oral contraceptives and the absolute risk of venous thromboembolism in women with single or multiple thrombophilic defects. Arch Int Med ;167:282-89.

4 van Vlijmen EFW *et al.,* (2011). Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception. Blood ;118:20551-61.

5 Jick *et al.* (1995) Risk of idiopathic cardiovascular death and non-fatal venous thromboembolism in women using roal contraceptives with differing progestagen components. Lancet;346:1589-93

6 Additional calculations based on Dinger *et al.,* (2007). The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception, 75 (5):344-35

The following table presents the MAH (originator)-sponsored phase-III clinical trials providing information on safety of the products. The total number of patients exposed in these studies amounts to 2455.

Table 1 Company-sponsored phase III clinical trials

Report no./Protocol no.	***Main objective (short title)***	***Duration of treatment***	***Treatment groups, No. of women (Full Analysis Set)***	***CPA/EE Women Years(WY)*****	***events***
6669 / 82009 (Basis of submission application)	Symptoms of androgenization	6-9 cycles	Diane-35: 218 Diane-50: 207	164 (D35) 155 (D50)	0
8186 / 83194 *Aydinlik et al., 1990*	Symptoms of androgenization Cycle control Contraceptive Efficacy	Up to 36 cycles	Diane-35: 1161	3483	0
13546 / JPH01293 Clinical study report 13546 / JPH01293 (1997)	Antiandrogenic effects	6 cycles	Diane-35: 20 Valette: 20 (0.03mg EE/2.0mg DNG)	10	0
AM80 / 93082 *Van Vloten et al., 2002*	Androgen related diseases	9 cycles	Diane-35: 43 Yasmin: 82 (0.03mg EE/3.0mg DRSP)	32	0
AI58 / 94162 *Clinical study report (1999)*	Acne vulgaris	9 cycles	Diane-35: 51 Developmental low-dose version of Diane-35*: 98	38 (D35) 74 (lowD)	1 VTE (lowD)
AM70 / 96010 *Clinical study report AM70 (1999)*	Hemostasis	6 cycles	Diane-35: 30 Developmental low-dose version of Diane-35*: 29	15 15 (lowD)	0
AM71 / 96011 *Clinical study report AM71 (1999)*	Lipid metabolism	6 cycles	Diane-35: 29 Developmental low-dose version of Diane-35*: 23	15 12 (lowD)	0
AS49 / 97082 *Cllinical study report AS49 (1999)*	Carbohydrate metabolism	6 cycles	Diane-35: 30 Developmental low-dose version of Diane-35*: 30	15 15 (lowD)	0
A18566 / 305547 *Clinical study report A18566 (2004)*	Acne papulopustulosa	6 cycles	Diane-35: 337 Diane-35+10 mg CPA:340 Pramino:334 (Day 1-7: 0.035 mg EE /0.180mg NGM); Day 8-14: 0.035mg EE / 0.215 mg NGM; Day 15-21: 0.035mg EE/0.25mgNGM)	169 170 (D+)	0
A28501 / 307760 *Palombo Kinne et al., 2009*	Acne papulopustulosa	6 cycles	Diane-35:537 Valette:525 (0.03mg EE/2.0mg DNG) Placebo:246	269	0

* Developmental low-dose version of Diane-35: Day 1-21: 0.02 mg EE/ 2.0 mg CPA; Day 22-28: 0.02 mg EE

** calculated as: (max number of cycles/13)
EE: Ethinylestradiol; DNG: Dienogest; DRSP: Drospirenone; CPA: Cyproterone acetate; NGM: Norgestimate

With exception of study report AI58 (low dose study), no cases of VTEs or ATEs were reported from the ten MAH- sponsored clinical trials with CPA/EE (2mg/0.035mg) in patients treated with CPA/EE (2mg/0.035mg). In study AI58, one patient in the CPA/EE (2mg/0.020 mg) treatment-arm 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) containing medicinal products. 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

The innovator MAH did not perform post-marketing safety surveillance studies with the primary focus on CPA/EE (2mg/0.035mg). However, 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 were 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 s 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) has an indication for contraception in women requiring treatment for androgen dependent 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 CPA/EE (2mg/0.035mg), conducted in Europe (Austria, Croatia, Germany, Italy, Poland, and Sweden) 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 (see table 2 below).

Table 2 CPA/EE (2mg/0.035mg) in INAS-OC

European study participants	22298	
Thereof users of CPA/EE-containing preparations	1672*	7.5%
Reason for use (as reported by patient)	N	%
Acne	983	58.8%
PCOS	25	1.5%
Other non-contraceptive reasons (e.g., cycle regulation)	140	8.4%
Contraception	469	28.1%
Total	1672	100.0%

* based on final data set as final report is under preparation

In this study, around 60% of women prescribed a CPA/EE (2mg/0.035mg)-containing preparation specifically reported in the baseline questionnaire that their CPA/EE 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 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 (see table 3 below) based on 6th Interim Report of this on-going study).

Table 3 CPA/EE (2mg/0.035mg) in INAS-SCORE

European study participants	20040	
Thereof users of CPA-containing preparations	1094	5.5%
Reason for use (as reported by patient)	N	%
Acne	690	63.1%
PCOS	39	3.6%
Other non-contraceptive reasons (e.g., cycle regulation)	128	11.7%
Contraception	221	20.2%
Reason missing	16	1.5%
Total	1094	100.0%

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 (2mg/0.035mg). In these studies VTE risk among CPA/EE (2mg/0.035mg) users was compared to the VTE risk of non-use as well as of various types of

COCs. No comparative safety data vs products that are registered for the treatment for acne/hirsutism/PCOS are presented.

There is overlap between the study populations of the three Lidegaard studies (DK1996-1998, 1995-2005, 2001-2009), as well as between the studies that used The General practice research database (GPRD) as a source (1992-1998 all users and acne/hirsutism/PCOS only). When calculating a pooled estimate of the crude incidence of VTE among CPA users, the Lidegaard (2009) study (DK1995-2005) and the Seaman (2003) study (acne/hirsutism/PCOS only) were therefore excluded. In the remaining cohort studies a total of 148 VTEs and 231165 WY CPA exposure were observed, corresponding to a pooled crude incidence of 64/100000 WY [95%CI 54-75 /100000].

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 exposed, was fatal.

Four studies presented adjusted relative VTE risks of CPA/EE vs non-use (see table 4).

Table 4 Pooled VTE risk of CPA/EE vs non-use from studies presenting adjusted relative risks.

Study	Reported relative risk estimate	[95%CI]	Relative weight in the pooled analysis	Relative weight in the pooled analysis
Lidegaard 2011	4.10	[3.34-4.99]	0.74	0.41
Seaman 2003	7.44	[3.67-15.08]	0.06	0.21
Hylckama Vlieg 2009	6.80	[4.70-10.00]	0.19	0.33
Parkin 2000	17.60	[2.70-113.00]	0.01	0.05
Pooled RR fixed effects	4.73	[4.00-5.61]	1.00	
Pooled RR random effects	5.88	[3.82-9.07]		1.00
P for homogeneity:	0.03			

Several observational studies (see table 5 below) have assessed the VTE risk with use of CPA/EE. 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 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.

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. In a recent study (Lidegaard 2012) the comparative analyses of the relative risk for thrombotic stroke and myocardial infarction between the various progestagens, including levonorgestrel, and non-use are in the same magnitude and do not show differences between the various progestagens. In addition, with regard to cyproterone acetate/ethinylestradiol vs. non-use statistical significance is even not achieved.

Table 5 Overview of observational studies on VTE and ATE risk associated with CPA exposure.

Name	Design	Sample	Events/exposed cases	Incidence in CPA	Relative risk vs non-use [95%CI]	Relative risk vs other COC [95%CI]
VTE						
Dinger 2007 [EURAS]	cohort PASS for Yasmin, AT BE DK FR DE NL UK, 2000-2004, all ages	4325 WY CPA 31415 WY LNG	4 CPA 25 LNG	92/100000 [25-237/100000]*	no	crude IRR vs LNG 1.16 [0.4-3.34]
Lidegaard 2003	cohort, Denmark, 1996-1998 , 15-44 yr	35675 WY CPA 160779 WY LNG	11 CPA 67 LNG	31/100000 [13-49/100000]	no	crude IRR vs LNG** 0.74 [0.39-1.40] Crude IRR vs any COC** 0.90 [0.49-1.63]
Lidegaard 2009	cohort, Denmark, 1995-2005, 15-44 yr	126687 WY CPA 367408 WY LNG	90 CPA 201 LNG	71/100000 [57-87/100000]*	Crude IRR** 2.36 [1.91-2.92] RR adj stratified <1yr 6.68 [4.50-9.94] 1-4yr 3.24 [2.28-4.61] >4yr 3.37 [2.38-4.76]	RR adj vs LNG 30-40µg 1.88 [1.47-2.42] 3rd/4th indirect. other vs LNG: norgestimate 1.19 (0.96 to 1.47). desogestrel 1.82 (1.49 to 2.22). gestodene 1.86 (1.59 to 2.18). drospirenone 1.64 (1.27 to 2.10)
Lidegaard 2011	cohort, Denmark, 2001-2009 , 15-44 yr	120934 WY CPA 104251 WY LNG	88 CPA 57 LNG (confirmed)	73/100000 [59-89/100000]*	RR adj 4.10 [3.34-4.99]	RR adj vs LNG 30-40µg 2.11 [1.51-2.95] 3rd/4th indirect. other vs LNG: Norgestimate 1.18 [0.86 to 1.62] Desogestrel 2.24 [1.65 to 3.02] Desogestrel 2.24 [1.65 to 3.02] Drospirenone 2.09 [1.55 to 2.82]
Seaman 2003	cohort+case-control, GPRD, 1992-1998, 15-39 yr, acne/hirsutism/ PCOS	28562 WY CPA 140203 WY conv COC	23 CPA 52 conv COC	80.5/100000 [51-121/100000]*	OR adj 7.44 [3.67-15.08]	age adj IRR vs conventional COCs 2.20 [1.35-3.58]
Seaman 2004	cohort+case-control, GPRD,1992-1998,	36432 WY CPA	25 CPA 349 conv	68.6/100000 [44-101/100000]*	**Indirect** *All users* OR adj no-use vs	*All users* OR adj vs

Name	Design	Sample	Events/exposed cases	Incidence in CPA	Relative risk vs non-use [95%CI]	Relative risk vs other COC [95%CI]
	15-39 yr (all women and subset acne/hirsutism/PCOS)	974805 WY conv COC	COC		conv COC 0.38 [0.31-0.46] **Indirect** *acne/hirsutism/PCOS* OR adj no-use vs conv COC 0.49 [0.14-1.74]	conventional COC 1.45 [0.80-2.64] *acne/hirsutism/PCOS* OR adj vs conventional COC 1.71 [0.31-9.49]
Farmer*** 1999/2000	cohort+case-control, GPRD 1992-1997, 15-49 yr	25709 WY CPA, 190191 WY LNG	16 CPA, 64 LNG	62/100000 [36-101/100000]*	no	crude IRR vs LNG 1.8 [0.9-3.2] OR adj vs LNG 1.4 [0.7-2.9]
Farmer*** 1999	cohort+case-control, UK Mediplus 1992-1997, 15-49 yr	8090 WY CPA, 49484 WY LNG	4CPA, 22 LNG	49/100000 [13-126/100000]*	no	OR adj vs LNG 0.7 [0.2-3.0]
Vasilakis 2001	nested case-control, GPRD 1992-1999, 16-39 yr	24401 CPA users 75000 LNG users	14 CPA (5PE, 7DVT) 12 LNG (5PE, 9DVT)	na	no	OR adj vs LNG 3.9 [1.1-13.4]
van Hylckama Vlieg 2009	case-control, NL, 1999-2004, 18-50yr	1524 cases 1760 controls	CPA 125 cases 62 controls LNG 485 cases 373 controls	na	OR adj 6.8 [4.7-10.0]	RR adj vs LNG 2.0 [1.3-3.0] 3rd/4th indirect. others vs LNG gestodene (1.6. 1.0 to 2.4) desogestrel (2.0. 1.4 to 2.8) drospirenone (1.7. 0.7 to 3.9)
Parkin 2000	case-control fatal PE, New Zealand 1990-1998, 15-49 yr	26 cases 111 controls	CPA 2 cases 1 control LNG 3 cases 8 controls	na	OR adj 17.6 [2.7-113];	indirect. OR adj vs non-use LNG 5.1 [1.2-21.4] Desogestrel/gestodene 14·9 (3·5–64·3)
Heuser 2004	case-control vs expected prevalence of use, New Zealand, 15-55yr	330 cases	CPA 15 cases LNG 25 cases	na	no	indirect. O/E use among cases: CPA: 1.93 LNG: 0.70 3rd gen: 1.36
Seaman 2006 (abstract)	case-control, GPRD, 15-39 yr, acne, hirsutism, PCOS	unknown	unknown	na	no	OR adj vs conventional COC 2.68 [1.03-6.95]
Tajmirrhiahi 2009 (abstract)	case-control, Iran, 18-56 yr	73 CVST cases 592 controls	unknown	na	OR CVST 35.54 [9.66-130.82]	Indirect OR low-dose OC vs non-use 7.56 [4.34-13.14]
Conard 2007 (abstract)	case-series	198 cases	CPA 55 cases	na	na	no
ATE						
Lidegaard 2012	cohort, Denmark, 1995-2009, 15-49 yr	187145 WY CPA 460599 WY LNG	CPA 29 thrombotic stroke, 12 MI;	stroke15,5/100000 [11-22/100000]* MI 6,4/100000 [3-11/100000]*	RR adj stroke 1.40 (0.97-2.03) MI 1.47 (0.83-2.61)	indirect. others vs non-use stroke: LNG 1.65 (1.39-1.95) Norgestim 1.52 (1.21–1.91) Desogestrel

Name	Design	Sample	Events/exposed cases	Incidence in CPA	Relative risk vs non-use [95%CI]	Relative risk vs other COC [95%CI]
			LNG 144 thromboti c stroke, 91 MI			2.20 (1.79–2.69) Gestodene 1.80 (1.58–2.04) MI: LNG 2.02 (1.63-2.50) Norgestim 1.33 (0.91–1.94) Desogestrel 2.09 (1.54–2.84) Gestodene 1.94 (1.62–2.33)
Dinger 2007 [EURAS]	See above	4325 WY CPA	0 ATE	0/100000 [0-85/100000]*	no	no

* Not provided in the publication, 95% confidence limits calculated by using Rothman's episheet->quickcalc->rate, exact CI for events ≤25

** Not provided in the publication, crude IRR and 95% confidence limits calculated by the assessor using Rothman's episheet -> rate data

*** Two publications identified from other MAH response: Hum Reprod Update 1999;5:688-706 reports an analysis of both GPRD and UK MediPlus; Br J Clin Pharmacol 2000;49:580-590 reports the same GPRD analysis, but sometimes corrected values. Results from year-of-birth controlled analyses were selected.

CVST: cerebral venous and sinus thrombosis, na: not applicable, conv: conventional, adj: adjusted, vs: versus, MI: myocardial infarction, CPA: cyproterone acetate containing COCs (Diane), LNG: levonorgestrel containing 2nd generation COCs, yr: year, WY: womenyears, VTE: venous thromboembolism, ATE: arterial thrombotic event, COC: combined oral contraceptive, OR: odds ratio, IRR: incidence rate ratio, PCOS: polycystic ovary syndrome, RR: relative risk.

Post-marketing reporting

Thromboembolic events are known, rare adverse drug reactions associated with the use of estrogen-progestagen containing preparations including CPA/EE (2mg/0.035mg). The thromboembolic risk is listed in the core company data sheet (CCDS) for CPA/EE and in the respective SmPCs.

The MAH (originator) has submitted in the annual PSURs for CPA/EE (2mg/0.035mg) information on thromboembolic events. As of last PSUR (PSUR No. 20, 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. This is less than the incidence of VTE as reported in epidemiological studies. A cumulative analysis presented below confirmed these rates, including reports received after cut-off.

In this analysis all cases from all worldwide sources received until 30 Jan 2013 were included. Standard hierarchical MedDRA SMQ embolic and thrombotic events (Level 1) released by MSSO for MedDRA version 15.1 and sub-analysis by event type (AT, VT, or mixed/unspecified) were used in three age groups: <18, 18-35, and >35 years of age at time of TE event. The total exposure was based on 75,417,345 women-years. The evaluation of compliance was compared with the CCDS, due to differences in SmPC recommendations

All retrieved cases were evaluated for the presence of at least one listed relevant risk factor for thromboembolic event (presence of listed contraindications, medical history, concomitant medication therapy (including indication) presented at time of treatment start, concomitant use of hormonal contraception, positive laboratory test results for inherited thrombophilias, age above 35 years, body mass index (BMI) higher than 30 kg/m^2 (or reported obesity as a concurrent condition).

- thrombotic and thromboembolic events

For the period since the global launch of CPA/EE through 30 Jan 2013, 968 cases (serious (93%) and non-serious (7%), medically confirmed (85%) and non-medically confirmed (15%) reporting thrombotic/thromboembolic events (TE) 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).

Of these 968 cases, 962 TE reports referred to female patients, 2 TE cases were reported in male patients and gender was not reported in 4 cases. 388 (40%) patients received CPA/EE for acne, hirsutism, alopecia or for otherwise documented treatment of symptoms of hyperandrogenism and for contraception in these patients. 233 (24%) patients used CPA/EE (2mg/0.035mg) for contraception alone, for 59 (6%) patients the product was prescribed for treatment of menstrual irregularities, uterine leiomyoma, ovarian cyst, ovarian disorder, endometriosis, or transsexualism (1 male patient) which are not listed indications. For 288 (30%) cases (including second male patient), information on therapy indication was not provided.

Table 6 VTE cases in the MAH's database, sorted by indication, cut-off date 6 Mar 2013 (from the line listing)

Indication labelled	**VTE**
Acne	149
PCOS	58
Hirsutism	23
Androgenic symptoms	22
Alopecia	8
Total	**260**
Indication off label	
Contraception	209
Menstrual cycle management	42
Menopause	3
Hypertrichosis	2
Labial abscess	1
Premenstrual syndrome	1
Uterine leiomyoma	1
Total	**259**
Unknown indication or not completed	292

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 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 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).

Of these 892 reports, 351 (39.3%) cases reported pulmonary embolism (PE) as a primary event; 162 (18.2%) reports described cerebral events; arterial events (such as myocardial infarction of retinal artery occlusion) were reported for 14 (1.6%) cases, and 268 (30%) cases described deep vein thrombosis (DVT) and other venous thrombotic and thromboembolic events. 97 (10.9%) cases reported embolic and thrombotic events, of unspecified vessel type or mixed arterial and venous.

Fatal cases

In total, 76 (7.9%) of 968 ADR reports with TE events reported cumulatively a fatal outcome (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 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.

Overview of cases reporting thrombotic / thromboembolic events

Table 7 gives an overview on case reports for CPA/EE (2mg/0.035mg) and corresponding global reporting rates and proportions for specific categories of cases retrieved with MedDRA SMQ Embolic and thrombotic events, displayed by age group.

Table 7 Overview of cases reporting thrombotic / thromboembolic events by age group – cumulative by fatality and risk factors (n=968)

Age group	Cases reporting any TE event n (%)	Reporting rate (per 100,000 women-years) all TE cases**	TE cases reporting fatal outcome n (%)*	Reporting rate (per 100,000 women-years) fatal TE cases**	TE cases with at least one risk factor identified n (%)*
Total	**968 (100%)**	**1.3**	**76 (7.9%)**	**0.1**	**317 (32.7%)**
Age < 18	88 (9.1%)	0.1	11 (1.1%)	0.01	14 (4.4%)
Age 18-35	639 (66%)	0.8	49 (5.1%)	0.06	138 (43.5%)
Age > 35	150 (15.5%)	0.2	10 (1%)	0.01	150 (47.5%)
Age Unknown	91 (9.4%)	0.1	6 (0.6%)	0.01	15 (4.7%)

* Proportions expressed in percentage of all cases retrieved with MedDRA SMQ "Embolic and thrombotic events" (n=968)
**Estimate based on global cumulative exposure of 75,417,345 women-years

In summary, global spontaneous reporting of TE in association with CPA/EE (2mg/0.035mg) is low at 1.3 per 100,000 women-years.

Arterial thrombotic and thromboembolic events (ATE)

A total of 52 (5.4%) of 968 retrieved cases reported one or more AEs from the sub-SMQ "Embolic and thrombotic events, arterial" in association with CPA/EE use.

This translates into reporting rate of 0.07 ADR reports with reactions represented in the sub-SMQ "Embolic and thrombotic events, arterial" 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. The overview on ATE case reports for CPA/EE (2mg/0.035mg) is presented below:

Table 8 Overview of cases reporting ATE by age group – cumulative by fatality and risk factors (n=52)

Age group	Cases reporting any ATE n (%)	Reporting rate (per 100,000 women-years) all ATE cases**	ATE cases reporting fatal outcome n (%)*	Reporting rate (per 100,000 women-years) fatal TE cases**	ATE cases with at least one risk factor identified n (%)*
Total	**52 (5.4%)**	**0.07**	**0**	**0**	**21 (22%)**
Age < 18	7 (0.7%)	0.009	n.a.***	n.a	3 (0.3%)
Age 18-35	29 (3%)	0.038	n.a	n.a	5 (0.5%)
Age > 35	12 (1.2%)	0.016	n.a	n.a	12 (1.2%)
Age Unknown	4 (0.4%)	0.005	n.a	n.a	1 (0.1%)

*Proportions expressed in percentage of all cases retrieved with MedDRA SMQ "Embolic and thrombotic events" (n=968)
**Estimate based on global cumulative exposure of 75,417,345 women-years
*** n.a. = not applicable

Venous thrombotic and thromboembolic events (VTE)

A total of 789 (81.5%) of 968 retrieved cases reported one or more AEs of venous thrombotic from the sub-SMQ "Embolic and thrombotic events, venous" in association with CPA/EE (2mg/0.035mg) use.

This translates into reporting rate of 1.05 ADR reports with reactions represented in the sub-SMQ "Embolic and thrombotic events, venous" 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.

Of these, 73 cases (out of 76 reported in total) had a fatal outcome related to VTE or VTE risk factors.

For the remaining 3 cases the cause of death was unspecified (see relevant section below). The overview on VTE case reports for CPA/EE (2mg/0.035mg) is given in the table below:

Table 9 Overview of cases reporting VTE by age group – cumulative by fatality and risk factors

Age group	Cases reporting any VTE n (%)	Reporting rate (per 100,000 women-years) all VTE cases**	VTE cases reporting fatal outcome n (%)*	Reporting rate (per 100,000 women-years) fatal TE cases**	VTE cases with at least one risk factor identified n (%)*
Total	**789 (81.5%)**	**1.05**	**73 (7.5%)**	**0.1**	**259 (26.8%)**
Age < 18	75 (7.7%)	0.10	10 (1.0%)	0.01	12 (1.2%)
Age 18-35	532 (55%)	0.71	48 (5.1%)	0.06	117 (12.1%)
Age > 35	119 (12.3%)	0.16	9 (0.9%)	0.01	119 (12.3%)
Age Unknown	63 (6.5%)	0.08	6 (0.6%)	0.01	11 (1.1%)

*Proportions expressed in percentage of all cases retrieved with MedDRA SMQ "Embolic and thrombotic events" (n=968)
**Estimate based on global cumulative exposure of 75,417,345 women-years

Unspecified and mixed arterial and venous TE cases

A total of 170 (17.6%) of 968 retrieved cases reported one or more AEs from the sub-SMQ “Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous” in association with CPA/EE use.

This translates into reporting rate of 0.23 ADR reports with reactions represented in the sub-SMQ “Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous” 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 170 reports of unspecified embolic and thrombotic events worldwide.

Of these, 10 cases reported fatal outcome, whereas 7 fatal cases overlap with cases selected in sub-SMQ “Embolic and thrombotic events, venous”. For 3 fatal cases (out of the 76 cases), origin of thromboembolic AEs was not specified.

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 company 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 onset dates of thromboembolic events reported to the company between 30 Jan 2013 and 06 Mar 2013 were provided for 155 of 175 cases, ranging from 1982 to Feb 2013. Of these 175 reports, 79 (45.1%) cases reported pulmonary embolism (PE) as a primary event; 35 (20%) reports described cerebral events; arterial events (such as myocardial infarction of retinal artery occlusion) were reported for 4 (2.3%) cases, and 26 (14.9%) cases described deep vein thrombosis (DVT) and other venous thrombotic and thromboembolic events. 31 (17.7%) cases reported embolic and thrombotic events of unspecified vessel type or mixed arterial and venous. Age was reported for 153 of 175 patients (mean 28.4 years, median 26 years). Risk factors or conceivable triggers for thrombotic / thromboembolic events (such as obesity, tobacco /alcohol abuse, recent injury / surgery or diabetes mellitus) were reported for approximately 34% of 175 patients. No new relevant safety information derives from the newly received reports after 30 Jan 2013.

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 (2mg/0.035mg) (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-progestagen containing preparations. An increased risk for thrombotic / thromboembolic events (that may be fatal in 1-2% of cases) is listed in the CCDS for CPA/EE (2mg/0.035mg).

Off Label Use

The MAH has defined the off-label use according to the therapeutic indications for CPA/EE 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. In order to find specific evidence regarding the incidence of off-label prescribing of CPA/EE (2mg/0.035mg) using information that was proposed by the PhVWP, the following issues were looked at:

The combination of cyproterone acetate (2 mg) + ethinylestradiol (0.035 mg) is positioned in expert practice guidelines and conference presentations as a treatment for androgen-dependent diseases such as acne which also has hormonal contraceptive properties.

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 (2mg/0.035mg) 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, page 4) suggest that CPA/EE (2mg/0.035mg) containing medicinal products 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) containing medicinal products relate to contraception and would appear, therefore, to be off-label use.

Two large, ongoing post-marketing surveillance studies (INAS-OC and INAS-SCORE) yield incidental data on the use of CPA/EE (2mg/0.035mg). These studies 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 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 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 in contraception from a total of 1094 users of CPA-containing preparations 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 hyperandrogenous conditions.

It is evident that in the IMS data, a large 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%. Thus although these figures are issued from a panel, the PRAC considers that of CPA/EE (2mg/0.035mg) containing medicinal products may be poorly prescribed in the main authorised indication (which is acne) and is also largely used as a contraceptive. Clarity on the indication is recommended.

Analysis of case reports in EudraVigilance

An analysis of the clinical risk factors reported in the case reports originating from EEA countries in Eudravigilance was considered. Additional analyses of the data were also performed, namely the analysis of reporting trends.

There were a total of 559 case reports where CPA/EE (2mg/0.035mg) was considered a suspect or interacting drug reported in the Eudravigilance until the 28th of February 2013; of these 34 had a fatal outcome. Most cases originated from France (120), Germany (118), the Netherlands (85), and Spain (60). Indications were acne (125 with 17 fatal), alopecia (8 with 1 fatal), and hypertrichosis (21 with 3 fatal); contraceptive methods female (178, 7 fatal), many different gynaecological problems (63 with 2 fatal), and unknown (184 with 9 fatal). The data as derived from the Eudravigilance database by the EMA are in line with the data as reported by the innovator MAH. No new trends were observed.

EMA drug utilisation study of CPA/EE (2mg/0.035mg) products

A study was conducted by the EMA to study the drug utilisation of cyproterone-ethinylestradiol products in IMS electronic health record databases from UK, France and Germany. The European Medicines Agency has access to three IMS prescribing databases, Germany (25 million patients), UK (5 million patients) and France (2 million patients). All three databases are representative for their respective countries and IMS databases have been utilised for analyses of co-prescribing, duration, indication of use, time trends and age distribution of users.

The following table summarises the reported indication for prescribing CPA/EE (2mg/0.035mg):

Table 10 Indication for prescribing CPA/EE (2mg/0.035mg)

	United Kingdom	**Germany**	**France**
All Rx	42401	191577	36815
Rx with ICD-10 code (N)	**42332**	**114336**	**24674**
Contraception	66.7%	61.5%	42.6%
Acne	12.4%	13.9%	8.2%
Hirsutism	1.0%	2.9%	0.3%
Polycystic ovarian syndrome	2.8%	1.2%	0.1%
Menstrual issues	2.6%	5.1%	0.5%
Ovarian dysfunction	-	0.6%	-
Androgen hypersecretion	-	6.1%	-
Hair loss (androgenic)	0.0%	1.5%	0.1%
Unspecified (adm. codes)	6.3%	0.2%	33.5%
Other	8.2%	7.1%	14.7%

It was noticed that CPA/EE (2mg/0.035mg) was for a large part not prescribed according to the recommendations in the SmPC. Contraception was the main indication for prescription, although this is not an approved indication if not concurrent with androgenic symptoms. However, it may very well be possible that androgen-related symptoms were present during prescription as a contraceptive. This can unfortunately not be derived from the data, possibly confounding the conclusion with regard to the extent of off-label use. Of the prescriptions, 11.9% (UK), 5.6% (DE), and 2.1% (FR) are prescribed

concomitant with a COC, despite a warning against concomitant use is included in the SmPCs of UK and DE.

Safety overview and discussion

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 the conclusions of the *ad hoc* expert group meeting and the stakeholders' submissions in particular with regards to the thromboembolic events.

To describe venous and thromboembolic effects from clinical studies with cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products only clinical studies that documented relevant adverse events were considered.

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

With exception of study report AI58(low dose study), no cases of VTEs or ATEs were reported from the ten MAH- sponsored clinical trials with cyproterone acetate/ethinylestradiol (2mg/0.020mg) containing medicinal products (CPA/EE) in patients treated with these products. In study AI58, one patient in the CPA/EE (2mg/0.035mg) treatment-arm developed VTE.

In 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) were 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). 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) has an indication for contraception in women requiring treatment for androgen dependent conditions.

With regards to 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 (2mg/0.035mg). 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 (2mg/0.035mg) 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 (2mg/0.035mg) is not significantly greater than for women on COCs.

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 information 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 levonorgestrel. Further to the PhVWP recommendation the PRAC re-emphasised in the SmPC that treatment should be withdrawn 3-4 cycles after the indicated clinical conditions have been completely resolved and that CPA/EE (2mg/0.035mg) not be continued solely to provide contraception.

Epidemiological studies have also suggested an association between the use of COCs in general and an increased risk of arterial 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 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 progestagens, including levonorgestrel, and non-use are in the same magnitude and do not show differences between the various progestagens. In addition, with regard to CPA/EE (2mg/0.035mg) vs. non-use statistical significance is even not achieved.

Based on the available data, no new and/or unexpected safety signal could be identified and the sponsor's assessment of the benefit-risk balance is favourable. The current body of scientific evidence supports a favourable benefit-risk profile for CPA/EE (2mg/0.035mg).

Post-marketing reporting

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

The MAH has submitted in the annual PSURs for CPA/EE (2mg/0.035mg) information on thromboembolic events. As of last PSUR 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. This is less than the incidence of VTE as reported in epidemiological studies.

All retrieved cases were evaluated for the presence of at least one listed relevant risk factor for thromboembolic event (presence of listed contraindications, medical history, concomitant medication therapy (including indication) presented at time of treatment start, concomitant use of hormonal contraception, positive laboratory test results for inherited thrombophilias, age above 35 years, body mass index (BMI) higher than 30 kg/m^2 (or reported obesity as a concurrent condition).

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 (TE) irrespective 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, consistent with the rate in the PSURs. 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.

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.

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 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.

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.

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. Of these, 73 cases reported fatal outcome.

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. From this consultation became 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.

Ad hoc expert group meeting

An *ad hoc* expert group meeting was convened on 26 April 2013 to respond to questions that PRAC requested. The nature of these questions was to clarify the clinical approach used regarding these medicines as well as the perception of the experts on the clinical effect. Specifically the PRAC wanted to know what additional information the experts would like to have in the product information to make clear the risks of thromboembolism with these medicinal products.

The experts that were consulted in the context of the *ad hoc* expert group meeting on CPA/EE (2mg/0.035mg) including patient organisation representatives recognised that VTEs can be difficult to diagnose and that non-specialist could have difficulties identifying a VTE and be unaware of the increased risk of women taking combined contraceptives and CPA/EE. It was also the patient's representative's view that patients are often not aware of this risk and that there may be lack of information from the prescriber to women about the risks associated with CPA/EE (2mg/0.035mg) and about the external additional risk factors. The experts also felt that there was lack of information to patients on the signs and symptoms of VTE and ATE.

2.1.2. Clinical efficacy

CPA/EE (2mg/0.035mg) containing medicinal products have strong anti-androgenic effects and their effects on hirsutism and seborrhoea has 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 (list of some relevant studies, see Table 11). The time to onset of efficacy is at least 3 months and the effects are more pronounced with longer treatment duration (and maximal after 12 months of treatment).

Table 11 List of studies in women with androgenic sensitive conditions

Reference	Type of Study	Study Medication	Study Population	Observation Period	Clinical Parameters
Greenwood *et al,.* 1985	randomized double-blind	Diane-35 vs. tetracycline	92 women with acne	6 months	sebum excretion rate
Carlborg 1986	multicenter comparative	Diane-35 vs Diane-50[1] vs Neovletta[2]	48 vs. 48 vs.	6 cycles	number of acne lesions,

Reference	Type of Study	Study Medication	Study Population	Observation Period	Clinical Parameters
		(EE/LNG)	37 women With at least 8 acne lesions before therapy		
Cavalli *et al.,* 1986	open, uncontrolled	Diane-35	35 women with acne, seborrhea and hirsutism of varying degree	15 months	clinical assessment acne, seborhea, hirsutism
Kaiser, 1986	open, uncontrolled	Diane-35	144 women with moderate acne and seborrhea	12 months	clinical assessment
DeCecco *et al.,* 1987	open, uncontrolled	Diane-35	24 women with mild to moderate acne, seborrhea, hirsutism	6 cycles	Subjective evaluation of therapeutic effect by patient
Falsetti *et al.,* 1987	open, uncontrolled	Diane-35	24 women with PCOS, 23 of these women had acne, seborrhea, hirsutism	24 cycles	clinical assessment of signs of andro-genization according to a score
Fugere *et al.,* 1988	Double-blind	Diane-35 vs Diane-50	80 women with acne, seborrhea and, in many cases, hirsutism	6 to 18 cycles	Clinical assessment by rating scale
Prelevic *et al.,* 1989	open, uncontrolled	Diane-35	46 women with PCOS and mild to severe hirsutism	9-30 cycles	assessment of hirsutism according to Abraham et 1976
Török *et al.,* 1990	open, uncontrolled	Diane-35	108 women with mild to severe acne and seborrhea	max 12 cycles	clinical assessment of severity, pregnancy rate
Erkkola *et al.,* 1990	open randomized	Diane-35 vs. Marvelon[3]	83 vs. 79 women with mild to severe acne, seborrhea, hirsutism	9 months	clinical assessment: symptoms not present, mild or severe, pregnancy rate
Fugere *et al.,* 1990	double-blind randomized	Diane-35 vs. Diane-50[1]	40 vs. 33 women with moderate to severe acne	12 cycles	different types of acne were assessed using the Cook`s method 1979
Barth *et al.,* 1991	double-blind randomized	Diane-35 vs Diane-35 plus 20 mg CPA vs Diane-35 plus 100 mg CPA	21 vs. 20 vs. 19 women with severe hirsutism	12 cycles	clinical assessment of hirsutism by Ferriman-Gallwey Ferriman Gallwey (FG) score 1961
Golland *et al.,* 1993	open, uncontrolled	Diane-35	32 women with PCOS, acne, hirsutism		clinical assessment of hirsutism by FG score
Dieben *et al.,* 1994	open, multicenter, randomized	Diane-35 vs. Gracial (biphasic EE/ Desogestrel)[4]	93 vs. 90 women with acne, at least 5 facial lesions	4 cycles	number of acne lesions clinical and photographic evaluation using grading system
Vegetti *et al.,* 1996	multicenter, randomized	Diane-35 vs Diane-35 plus Goserelin[5]	26 vs. 24 women with hirsutism and acne	12 cycles plus 6 cycles follow up	subjective and objective evaluation of hair growth, mean hair diameter, visual assessment of acne
Charoenvisal *et al.*, 1996	Open label, bi-center, randomized	Diane-35 vs. Marvelon (EE/DSG)	32 (Marvelon), 34 (Diane)	6 cycles	Objective and subjective severity of acne
Gökmen *et al.,* 1996	randomized open-label active controlled	Diane-35 vs. Diane-35+CPA 100mg during day 1-10	210 patients with PCOS 48 vs.	6 months	FG score

Reference	Type of Study	Study Medication	Study Population	Observation Period	Clinical Parameters
		vs. ketoconazole vs. spironolactone	65 vs. 16 vs. 12 Hirsutism		
Falsetti et al. 1997	open, uncontrolled	Diane-35	82 women with PCOS, acne and hirsutism	48 cycles	number of acne lesions, assessment of hirsutism by FG score
Castelo-Branco *et al.,* 1997	open, controlled	Diane-35 vs Marvelon[3] plus triptorelin[6] (3.75 mg)	25 vs. 23 women with severe hirsutism	12 cycles	assessment of hirsutism by FG score
Carmina *et al.,* 1997	open, controlled	Diane-35 vs. Diane-35 plus 50 mg CPA vs. Decapeptyl[6] (3.75 mg) plus 0.625 mg conj. estrogens plus 10 mg MPA[7]	20 vs 20 vs. 20 women with hirsutism	12 cycles	assessment of hirsutism by FG score
Acien *et al.,* 1997	open, controlled	Diane-35 vs Diane-35 plus triptoreline[6] (3.75 mg)	12 vs. 12 women with PCOS, acne, seborrhoea hirsutism	10 cycles	assessment of hirsutism by FG score
Sahin *et al.,* 1998	open, randomized	Diane-35 vs finasteride (5 mg)	21 vs. 21 women with hirsutism	9 months	assessment of hirsutism by FG score
Kelestimur *et al.*, 1998	open, randomized	Diane-35 vs Diane-35 plus spironolactone (100 mg)	22 vs. 28 women with hirsutism	12 months	assessment of hirsutism by FG score
Gollnick *et al.,* 1998	open, multicenter, uncontrolled	Diane-35	890 women with grade I-IV facial acne according to Plewig and Kligman the majority had acne tarda	6 cycles	number of acne lesions, assessment of seborrhea and hirsutism
Tartagni et al. 2000	randomized, single-blind	Diane-35 vs Diane-35 plus finasteride (5 mg)	25 vs. 25 women with idiopathic hirsutism or PCOS	6 months	assessment of hirsutism by FG score [6]
Vartiainen *et al.*, 2001	open, randomized	Diane-35 vs. Gracial[4] (biphasic EE/DSG combination)	88 vs. 84 women with mild to severe acne	6 cycles	number of acne lesions: comedones, papules, pustules, nodules, subjective and objective scores
Sahin *et al.*, 2001	open, randomized	Diane-35 vs Diane-35 plus finasteride (5 mg)	20 vs. 20 women with hirsutism	12 months	assessment of hirsutism by FG score
Falsetti *et al.*, 2001	open, uncontrolled	Diane-35	140 women with PCOS, moderate or severe acne, hirsutism	60 cycles	number of acne lesions, assessment of hirsutism by FG score
Elter *et al.,* 2002	randomized open	Diane-35 vs. Diane-35 + metformine	20 vs. 20 non obese women with PCOS 16-36 years with hirsutism	4 months	FG score
J&J, 2005	Double-blind randomized	Diane-35 vs TriCilest[11]	48 women with acne vulgaris gr. II or III	3 cycles	Change in total lesion count

Reference	Type of Study	Study Medication	Study Population	Observation Period	Clinical Parameters
		(triphasic EE/NGM)			
Luque-Ramirez, 2007	randomized open	Diane-35 vs Metformine	15 vs 19 women with PCOS	6 months	hyper-androgenism symptoms FG score
Batukan et al. (2007)	randomized open	Diane-35 Vs. Yasmin[12]	91 (43 vs. 48) patients with moderate to severe hirsutism	12 months	clinical hirsutism FG scores
Wu, 2008	randomized open	Diane-35 21 d/month vs. Metformine vs. Diane-50 + metformine	20 vs. 20 vs. 20 women with PCOS Hirsutism	3 months	hyper-androgenism FH scores
Cetinkalp, 2009	randomized open	Metformine vs Rosigliatazone vs Diane-35	47 vs 14 vs 33 women with PCOS	4 months	hyper-androgenism symptoms as acne, FG score, menstrual disorders
Naka, 2011	open pilot study	Diane-35	13 non-obese women with PCOS and hyper-andro-genism; comparative group of 14 matched healthy women	6 months	hyper-androgenism FH scores
Ibanez, 2011	randomized open	Diane-35 vs. low dose of plioglitazone flutamide metformine	17 vs. 17 women with hyper-insulinemic androgen excess	6 months	hirsutism and acne scores;
Bhattacharya,2012	double-blind randomized controlled	Diane-35 vs. Novelon[13]; 30 µg EE/150 µg DSG vs. Yasmin[12]	58 vs. 56 vs. 57 patients with PCOS hirsutism	12 months	Hirsutism score (modified FG score), acne and acanthosis nigricans scores

Table notes:

1 Diane-50: 2mg cyproterone acetate plus 0.05mg ethinylestradiol
2 Neovletta: 0.15mg levonorgestrel plus 0.03mg ethinylestradiol
3 Marvelon: 0.15mg desogestrel plus 0.03mg ethinylestradiol
4 Gracial: biphasic combination with 0.025mg desogestrel plus 0.04mg ethinylestradiol for 7 days and 0.125mg desogestrel plus 0.03mg ethinylestradiol for 15 days with a 6 day pill free period
5 Goserelin: GnRH analogue Zoladex 3.6mg
6 Triptorilin: GnRH analogue Decapeptyl 3.75
7 MPA: Medroxyprogesterone acetate
8 Yasmin: 3mg drospirenone plus 0.03mg ethinylestradiol
9 Pramino: triphasic combination of 0.18mg norgestimate plus 0.035mg ethinylestradiol for 7 days, 0.215mg norgestimate plus 0.035mg ethinylestradiol for 7 days and 0.25mg norgestimate plus 0.035mg ethinylestradiol for 7 days
10 Valette: 2mg dienogest plus 0.03mg ethinylestradiol
11 TriCilest: (noregestimate plus ethinylestradiol), 0.18mg-0.035mg or 0.215mg-0.035mg or 0.25mg-0.035mg
12 Yasmin: 3 mg DRSP/30 mg EE
13 Novelon; 30 µg EE/150 µg DSG

a. Treatment of hirsutism

For the treatment of hirsutism alone (mostly in PCOS patients), 13 studies demonstrated efficacy versus other treatments (including comparisons with off-label 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 equal 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.[7] This is expected in view of the differences in anti-androgenic properties of cyproterone, drospirenone and desogestrel.

Cyproterone has the strongest anti-androgen activity (see table below):

Table 12 Biological activities of natural progesterone and synthetic progestagen

Table 2
Biological activities of natural progesterone and synthetic progestins

Progestin	Progesto-genic	Anti-gonado-tropic	Anti-estrogenic	Estro-genic	Andro-genic	Anti-andro-genic	Gluco-corticoid	Anti-mineralo-corticoid
Progesterone	+	+	+	−	−	±	+	+
Dydrogesterone	+	−	+	−	−	±	−	±
Medrogestone	+	+	+	−	−	±	−	−
17α-Hydroxy-derivatives								
Chlormadinone acetate	+	+	+	−	−	+	+	−
Cyproterone acetate	+	+	+	−	−	++	+	−
Megestrol acetate	+	+	+	−	±	+	+	−
Medroxy-progesterone-acetate	+	+	+	−	±	−	+	−
19-Nor-progesterone-derivatives								
Nomegestrol acetate	+	+	+	−	−	±	−	−
Promegestone	+	+	+	−	−	−	−	−
Trimegestone	+	+	+	−	−	±	−	±
Spirolactone-derivatives								
Drospirenone	+	+	+	−	−	+	−	+
19-Nortestosterone derivatives								
Norethisterone	+	+	+	+	+	−	−	−
Lynestrenol	+	+	+	+	+	−	−	−
Norethinodrel	±	+	±	+	±	−	−	−
Levonorgestrel	+	+	+	−	+	−	−	−
Norgestimate	+	+	+	−	+	−	−	−
3-Keto-desogestrel	+	+	+	−	+	−	−	−
Gestoden	+	+	+	−	+	−	+	+
Dienogest	+	+	±	±	−	+	−	−

Taken from reference [5,7,8,10–15]. (+) effective; (±) weakly effective; (−) not effective.

Source: Adolf, E., Schindler, Jorge R. Pasqualini E, Karl W. Schweppef, Jos H. H. Thijssen, Classification and pharmacology of progestins, Maturitas 46S1 (2003) S7–S16

In the Cochrane review[8] 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 this 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 drug therapies (spironolactone, finasteride, gonadotropin-releasing hormone- (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

[7] Bhattacharya SM, Jha A. (2012), Fertil Steril. Oct;98(4):1053-9.
[8] van der Spuy ZM, Le Roux PA, Matjila MJ. Cyproterone acetate for hirsutism (Review) (2009). The Cochrane Library.

The data on efficacy of CPA/EE in alopecia androgenetica, except for the mechanism of action, is limited to one small study in which some limited beneficial effects were noted.[9]

d Acne without androgenic features

Regarding acne without androgenic features, one study compared CPA/EE (2mg/0.035mg) with systemic antibiotic tetracycline and showed similar efficacy[10]. Two studies comparing CPA/EE (2mg/0.035mg) with dienogest containing combined oral contraceptive and with norgestimate containing combined oral contraceptive also showed similar efficacy[11,12].

Two studies compared CPA/EE (2mg/0.035mg) with levonorgestrel/EE (LNG/EE).[13] 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 (2012)[14], which evaluated efficacy of combined oral contraceptives in acne, reported that regarding the differences in the comparative effectiveness of the contraceptives, data were 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 effects

The contraceptive effects of CPA/EE (2mg/0.035mg) were investigated in studies submitted during the request for marketing authorisation.

The overall Pearl Index for CPA/EE 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[15].

Table 13 Pearl Index based on CPA/EE 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.

9 DeCecco L, Capitano GL, Bertolini S, Croce S, Centonze A. Clinical and metabolic effects of a new estrogen-antiandrogen low dose combination. New Developments in Biosciences 3, Berlin, New York, Walter de Gruyter (1987), p167-173

10 Greenwood R, Brummitt L, Burke B, Cunliffe WJ. (1985). BMJ; 291: 1231-1235

11 Clinical Study Report No A18566 (2004, Multicenter, double-blind, randomized parallel group study on efficacy of 0.035 mg ethinylestradiol/ 2mg cyproterone acetate and of 0.035 mg ethinylestradiol/ 2mg cyproterone acetate in combination with 10 mg cyproterone acetate in comparison to triphasic ethinylestradiol/ norgestimate over 6 cycles in women with acne papulopustulosa.

12 Palombo-Kinne E, Schellschmidt I, Schumacher U, Gräser T. Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate. (2009) Contraception. Apr; 79(4):282-9.

13 Carlborg L (1986)Acta Obstet Gynecol Scand Suppl,134:29-32.

14 Arowojolu AO, Gallo MF, Lopez LM, Grimes DA.Combined oral contraceptive pills for treatment of acne. Cochrane database of systematic reviews (2012), issue 107

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

In addition the contraceptive effect of CPA/EE (2mg/0.035mg) was investigated in a EURAS study. The comparison of Pearl Indices in the EURAS study demonstrated the Pearl Index of (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 in this study) (see table below).

Table 14 Unintended pregnancies, exposure, Pearl Indices and 95% confidence intervals for four specific progestagen/ethinylestradiol combination

	All Age Groups				Age 18 - 35			
Regimen	Preg.*	Exp.**	PI°	95% CI°°	Preg.*	Exp.**	PI°	95% CI°°
CPA/EE	15	56,134	0.35	0.19 - 0.57	12	41,974	0.37	0.19 - 0.65
LNG/EE	36	89,267	0.52	0.37 - 0.73	28	61,689	0.59	0.39 - 0.85
GSD/EE	4	10,639	0.49	0.13 - 1.25	4	8,217	0.63	0.17 - 1.62
LNG/EE seq.	20	59,323	0.44	0.27 - 0.68	15	40,552	0.48	0.27 - 0.79

* number of unintended pregnancies; ** exposure in cycles; ° Pearl Index; °° 95% confidence interval
LNG: levonorgestrel; GSD: gestodene

In conclusion, these data demonstrated that CPA/EE (2mg/0.035mg) has adequate contraceptive effect which is comparable with other approved combined hormonal contraceptives

In addition a total of 829 post-marketing spontaneous reports on unintended pregnancies were reported which contributed with 6% of the total number of ADR reports received cumulatively for CPA/EE (2mg/0.035mg) until 30 January 2013 (n=13,875 in total). This translates into an overall pregnancy reporting rate of 0.001 per 100 women-years, based on the estimated cumulative patient exposure of 75,417,345 women-years. These data reflect a very low pregnancy reporting frequency.

Efficacy overview and discussion

CPA/EE (2mg/0.035mg) containing medicinal products have anti-androgenic effects and their 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 onset of efficacy is at least three months and the effects are more pronounced with longer treatment duration (and maximal after 12 months of treatment).

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 equal 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, a significantly improved Ferriman Gallwey (FG) score at 12 months was found when cyproterone acetate was compared with flutamide in combination with a COC). Otherwise no clinical differences in hirsutism were detected when CPA/EE (2mg/0.035mg) was compared to monotherapy with CPA and several experimental drug therapies (spironolactone, finasteride, GnRH analogues, ketoconazole). 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.

The data on efficacy of CPA/EE (2mg/0.035mg) in alopecia androgenetica, except for the mechanism of action, is limited to one small study in which some beneficial effects were noted.

Regarding acne without androgenic features, one study compared CPA/EE (2mg/0.035mg) with systemic antibiotic tetracycline and showed similar efficacy. Two studies 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 which evaluated efficacy of combined oral contraceptives in acne, reported that regarding the differences in the comparative effectiveness of the contraceptives, data were 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.

The contraceptive effects of CPA/EE (2mg/0.035mg) were based on studies submitted during the request for marketing 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. In addition the contraceptive effect of CPA/EE (2mg/0.035mg) was investigated in a 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 in this study).

In conclusion the efficacy in acne with or without seborrhoea and in hirsutism is well established by the data provided. In addition the CPA/EE (2mg/0.035mg) containing medicinal products demonstrate contraceptive effects.

2.2. Risk minimisation activities

Risk management plan

No risk management plan (RMP) is in place for CPA/EE (2mg/0.035mg) as there has been no regulatory authority request or MAH concern which would have required the preparation of a Risk Management Plan for these medicinal products. Routine pharmacovigilance has been conducted since first marketing authorisation and safety information summarised in the core company data sheet

(CCDS). The PRAC recommended that a core RMP should be submitted to the national competent authorities for assessment.

Changes to the Product Information

Extensive advice is given in the product labelling of CPA/EE (2mg/0.035mg) regarding the risk for venous and arterial thromboembolic events, including information in the sections special warnings and precautions for use and the section contraindication. This is considered the most appropriate way to communicate the risks related to CPA/EE (2mg/0.035mg), including the risk for VTE and ATE.

CPA/EE (2mg/0.035mg) medicinal products are licenced in all member states of the EU as well as in Iceland and Norway, starting with Germany in 1985. Previously the PhVWP agreed on a wording for SmPCs with respect to the risk of venous thromboembolism (VTE). That wording was implemented in 11 of the 15 member states that comprised the EU at that time and has since been adopted by a further 5 countries that have subsequently acceded to the European Union.

In addition to already agreed previous wording the PRAC considered there was a need to strengthen the information in the SmPC and therefore recommended review of the wording of the indication for clarity, new contraindications and warnings. The PRAC recommends that all relevant sections of the product information (PI) should be updated and the wording regarding thromboembolism should be the one adopted during this referral procedure. Further discussion on the relevant sections of the PI follows further below in the corresponding section of this report.

Information and awareness of the Healthcare professionals

Some epidemiological data clearly show a lack of consideration by prescribers of the contraindications, warnings and precautions with respect to thromboembolic risk, and off-label prescription. Educational measures are necessary in order to recall appropriate prescription practices to the concerned healthcare professionals.

i. DHPC and Communication action plan

A direct healthcare professional communication (DHPC) has been discussed and agreed during the assessment of these medicinal products to inform the healthcare professionals on the changes to the PI and on the thromboembolic risk with these products

ii. Educational Material

PRAC also recommended that educational material should be issued specifically targeting to inform the professionals on the risks of thromboembolism as well on the patient population who better benefit from these medicinal products and to use these medicinal products strictly within the limits of prescription.

Information and awareness of patients

The PRAC also recommended additional information to highlight the risks and warnings of thromboembolism and to make the women aware of the symptoms of these adverse events in order to contribute in the early diagnosis of such events.

Future Monitoring

Healthcare providers (health insurances, state health systems) have a monitoring role to play concerning appropriate prescription practices. For example, inappropriate long-term prescription of CPA/EE (2mg/0.035mg) to individual patients can be detected through electronic systems if such systems are in place.

i. Drug utilisation study (DUS)

In order to better understand the potential extent of inappropriate prescribing of CPA/EE containing medicinal products, the MAH is proposing to conduct a drug utilisation study (DUS). This drug utilisation study should aim to collect the reasons for the prescription of these products in a prospective study design with a special focus on the clinical decision making process. Questionnaires are one potential tool for data collection on drug utilisation and widely used.

The PRAC has endorsed the proposal for the prospective DUS. The protocol of this study should be submitted within the risk management plan for agreement with the national competent authorities of the Member States.

ii. Post-authorisation safety study (PASS)

A post-authorisation safety study to evaluate the effectiveness of the risk minimisation activities was recommended by the PRAC. The protocol of this study should be submitted within the risk management plan for agreement with the national competent authorities of the Member States.

2.3. Product information

The PRAC recommended the amendments to be introduced in the summary of product characteristics (SmPC) and package leaflet (PL).

Summary of Product Characteristics

Section 4.1 Therapeutic indication

The new adopted indication is:

> *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, <product name> should only be used after topical therapy or systemic antibiotic treatments have failed.*
>
> *Since < product name>is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3).*

Section 4.2 Posology and methods of administration

In this section a note was added in the sub-heading 'Duration of use' for the need of the periodic evaluation of the treatment by the physician and that the time to relief of symptoms is at least three months.

Section 4.3 Contraindications

The PRAC concluded that the products should not be used concomitantly with other hormonal contraceptives due to their contraceptive efficacy. Cyproterone acetate/ ethinylestradiol (2mg/0.035mg) containing medicinal products should be contraindicated in patients with history or hereditary predisposition of venous thrombosis and to patients with presence of a severe or multiple risk factors for VTEs or ATEs.

Section 4.4 Special warnings and precautions for use

The PRAC also recommended for warnings to be included in this section. More specifically a list in the circulatory disorders presents the risks of thromboembolic events. In addition it lists the symptoms of VTEs and ATEs for further awareness. It is well known that the risks of VTEs increases with age, obesity and prolonged immobilization, whereas major risk factors for ATE are smoking, obesity, hypertension and diabetes and these are presented in this section of the SmPC. 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 symptoms is at least three months.

Section 4.8 Undesirable effects

This section was amended to include the new adverse events

Package Leaflet

The package leaflet was aligned to the SmPC proposals.

2.4. Benefit-risk assessment

According to most of the clinical experts involved in the ad-hoc expert group, CPA/EE (2mg/0.035mg) has a place in the therapeutic range for the treatment of acne, particularly in women who require contraception. Some considered however that such treatment should only be prescribed if topical therapy or systemic antibiotic treatments have failed.

Some experts recommended restriction of use to women under 40 years of age and all agreed that CPA/EE (2mg/0.035mg) should be totally contra-indicated in combination with other combined hormonal contraceptives.

The experts also proposed that more information is given in the package leaflet on any additional cardiovascular risk factors (such as smoking, long-haul flights, high altitude climbing).

After reviewing all the available data and taking into consideration the conclusions of the ad-hoc expert group meeting, 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 are hormonal contraceptives and as such the concomitant use with another hormonal contraceptive is contraindicated. This conclusion is subject to the restrictions, warnings, changes to the product information, additional pharmacovigilance activities and risk minimisation measures agreed.

The Committee also concluded that the benefit-risk balance of CPA/EE (2mg/0.035mg) containing products is no longer favourable in the treatment of alopecia and that this product should no longer be used in this indication due to the increased TE risk and the very limited data regarding the efficacy in this indication.

2.5. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, and the conclusions of the Ad-Hoc Expert meeting, the PRAC concluded that the marketing authorisation holder(s) should sponsor a post-authorisation safety study together with the follow up evaluation of the results of that study; the marketing authorisation holder should implement risk minimisation measures; and 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 risk management plan (RMP) within a certain timeframe. The protocol of drug utilisation study in order to 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 products 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, changes to the product information, additional pharmacovigilance activities and additional risk minimisation measures agreed.

3. Communication plan

The PRAC considered that a Direct Healthcare Professional Communication (DHPC) was needed to communicate on the measures taken for the safe use of these medicinal products and on the risk of thromboembolism.

Relevant European healthcare professional organisations were consulted and provided input on the draft DHPC. The final version of this DHPC agreed by the PRAC is provided together with the communication plan (see attachments to this report).

The MAH should agree the translations and local specificities of the DHPC with national competent authorities. As the prescribing physicians vary from country to country they must be adapted accordingly e.g. general practitioners, dermatologists, gynaecologists, endocrinologists. Differences in target populations by Member State need to be discussed and aligned with the National Competent Authorities.

4. Conclusion and grounds for the 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, recommends by a majority of 31 out of 32 votes 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 measure(s);

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).

Appendix 1

Listing of submissions of all data received by the Agency

Listing of submissions of all data received by the Agency (i.e. from MAHs and other stakeholders) for cyproterone acetate / ethinylestradiol (2mg / 0.035mg) containing medicinal products

Submission
MAHs
Adamed
Almirall
Bayer HealthCare
Cipla UK
Dermapharm (Acis, Sun-Farm)
Effik
Gynial
Laboratoires Majorelle
Mithra
Mylan
Stragen
Teva
UCB Pharma
Zentiva & Sanofi
Stakeholders
Patient
Patient
Patient
Patient
Charity (2 submissions)
Gynaecologist / Nuclear Medicine and Internal medicine
Patient
Anonymous

Appendix 2

Divergent positions to PRAC recommendation

Article 107i of Directive 2001/83/EC

Procedure No: EMEA/H/A-107i/1357

Cyproterone acetate/ethinylestradiol (2mg/0.035mg) containing medicinal products

Divergent statement

The undersigned PRAC member, representative of the French National Competent Authority, co-rapporteur for the dossier, has a divergent opinion with the PRAC's recommendation on medicines containing cyproterone acetate 2 mg (CPA) / ethinylestradiol 0.035 mg (EE) (Diane and generics).

The reasons for divergent opinion are as follows:

- With respect to risk:

Since 1987, thromboembolic events were reported including fatal cases (8% of the cases reported) associated with CPA/EE mainly within the first year of treatment. Venous thromboembolism (VTE) is the most reported effect.

The PRAC member highlights that the PRAC agrees with the conclusion of an increased risk of thromboembolic events (VTE), 4 to 7 higher in female users of a combination of CPA/EE than in female non-exposed to CPA/EE or Combined Oral Contraceptives (COCs) and that this risk is assumed to be equivalent to that of non levonorgestrel COCs.

- With respect to benefit:

The assessment of the data provided during this referral shows a thin evidence of the efficacy of the product in acne and difficulties to qualify the type of acne due to the lack of standard method of acne grading used in clinical trials.

With regard to contraception, although there is a presumption of efficacy for CPA/EE as a contraceptive considering the pharmacological properties of both components, the level of efficacy demonstration is insufficient to grant an indication in contraception. The efficacy studies performed are not up to nowadays' standards.

Even if the PRAC recommendation is in favour of a positive benefit/risk ratio provided changes of the product information (SmPC and Package Leaflet), a communication plan including educational materials and two studies, a post-authorisation study and a drug utilisation study, the above Member state is of opinion that the MAHs should provide a clinical study with a robust methodology to allow the calculation of a reliable Pearl Index in order to prove its full efficacy as a contraceptive.

Diane is also indicated in hirsutism and alopecia in several EU Member States. However, there are no robust data to support these indications.

The therapeutic fields of CPA/EE containing products are heterogeneous across Europe and this unclear situation participates to the risk of incorrect handling of the drug.

- With respect to off-label use:

Data issued from French and European panel of physicians confirm the off-label use of CPA/EE containing products as a contraceptive only. Responses from patients also support this large off-label use.

The confusion remains about the labelling of indications, especially for the contraceptive effect leading to a wide off-label use exposing unnecessarily women for a longer period to an increased risk of venous thromboembolism.

Taking all these aspects into account, the benefit / risk balance of Diane 35 and other medicines containing cyproterone acetate 2 mg (CPA) / ethinylestradiol 0.035 mg (EE) is unfavourable as regards the therapeutic indications in androgen increased-sensitivity women for whom hormonal contraceptive treatment is considered appropriate.

In consequences, the above Member State expresses a divergent opinion to the proposed labelling for the therapeutic indications.

PRAC member expressing a divergent position

Isabelle Robine (FR)	16 May 2013	Signature: ……