Annex IV

Scientific conclusions and grounds for the variation to the terms of the marketing authorisations, and detailed explanation for the differences from the PRAC recommendation

CHMP Members' Divergent Positions

Scientific conclusions and grounds for the conclusions

The CHMP considered the below PRAC recommendation dated 10 October 2013 with regards to combined hormonal contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, norelgestromin, norgestimate or nomegestrol.

1 – Overall summary of the scientific evaluation

Medicinal products containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, norelgestromin, norgestimate or nomegestrol are authorised in the European Union as combined hormonal contraceptives (CHCs). These are combined with varying doses of ethinylestradiol (EE) or with estradiol (E2).

In February 2013, the French medicines agency (ANSM) initiated a referral procedure under Article 31 of Directive 2001/83/EC on the basis that the benefit-risk balance of these combined hormonal contraceptives had become unfavourable in the currently authorised indication of contraception due to the increased risk of thromboembolism (TE) and therefore it was in the interest of the Union to refer the matter to the PRAC. The PRAC was requested to give a recommendation on whether the indication of medicinal products containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, norelgestromin, norgestimate or nomegestrol combined with an oestrogen (ethinylestradiol or estradiol) should be restricted and/or any other regulatory measure(s) taken.

The PRAC reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, as well as the views of an *ad hoc* expert meeting on the efficacy and safety of the CHCs, in particular in relation to the risk of thromboembolism.

Thromboembolic events are adverse events which usually occur in a vein of the leg (deep vein thrombosis, DVT). When diagnosis is not made and no treatment is started, or when clear symptoms of thrombosis are not identifiable, the clot can move upwards to the lung (pulmonary embolism, PE) or the brain (cerebral embolism, CE). Misdiagnosis is possible, since TE presents with diffuse symptoms and is a rare event in a population of healthy young women. Overall, venous thromboembolic events (VTE) could be fatal in 1-2% of the cases. Known risk factors for VTE include history of VTE, pregnancy, trauma, surgery, immobilisation (e.g. after surgery or long flights), obesity and smoking (i.e. all situations of a pro-thrombotic state). Also there are certain hereditary thrombophilic defects that increase the risk. Checking personal and family history of VTE before prescribing combined CHC medicinal products is, therefore, recommended in the product information of the products.

Many studies have evaluated the risk of VTE and its complications (deep vein thrombosis, pulmonary embolism) among users of different CHCs. The current review confirmed the previous understanding that the level of VTE risk with CHCs containing low dose of ethinylestradiol (ethinylestradiol <50µg) is small, but differences in the VTE risk were observed between most products depending on the type of progestogen they contain. Based on the totality of the available data the PRAC concluded that the risk of VTE differs between products - with the lower risk products being those containing the progestogens levonorgestrel, norethisterone and norgestimate. For some products (i.e. chlormadinone, dienogest, nomegestrol) there are currently insufficient data to establish the risk compares with the lower risk products. For chlormadinone this will be investigated through a post-authorisation safety study, which is further discussed below. For dienogest and nomegestrol studies are on going and results will be submitted when available.

The risk of VTE with CHCs differs among products depending on the type of progestogen they contain. Having assessed all the available data, the PRAC concluded that:

- The estimated incidence of risk is lowest with the CHCs containing the progestogens levonorgestrel, norgestimate and norethisterone: it is estimated that each year there will be between 5 and 7 cases of VTE per 10,000 women who use these medicines.
- The estimated incidence of risk is higher with the progestogens etonogestrel and norelgestromin, with between 6 and 12 cases yearly per 10,000 women.
- The estimated incidence of risk is also higher with the progestogens gestodene, desogestrel, drospirenone, with between 9 and 12 cases yearly per 10,000 women.
- For CHCs containing chlormadinone, dienogest and nomegestrol, the available data are insufficient to know how the risk compares with the other CHCs.

For comparison, in women who are not using CHCs (no-users) and who are not pregnant, there will be around 2 cases of VTE each year per 10,000 women.

It has been shown that risk of VTE is highest during the first year a woman starts hormonal contraceptives or when she re-starts after a period of non-use of at least one month (Dinger *et al,*. 2007, Sidney *et al.,* 2013). After an initially higher risk during the first year of use, the risk decreases to a constant lower level. The risk of VTE is also higher in the presence of intrinsic risk factors. Considering that risk factors for VTE change over time the PRAC noted that an individual's risk should be re-evaluated periodically.

It is known that the risk of arterial thromboembolism (ATE) (myocardial infarction, cerebrovascular accident) is also increased with use of CHCs, however there was no evidence for differences between CHCs in their relative risk of ATE.

Therefore, on the basis of the available evidence, the PRAC acknowledged that the benefits associated with using a CHC far outweigh the risk of serious adverse events in most women. There was no evidence for differences between these medicinal products in terms of beneficial effects. However, the PRAC recommended routine risk minimisation measures, including a strengthening of the wording of the product information to reflect the current knowledge of risks (incidence rate) as well as symptoms for VTE and ATE and clarifying the situations for which these products are contraindicated. In particular, these medicinal products should be contraindicated in patients with multiple risk factors, in patients after major surgery with prolonged immobilisation, patients who smoke and patients with history or hereditary predisposition of thromboembolism. Furthermore, proactive information to communicate the outcome of the present review and to highlight the risk of the thromboembolic events through a direct healthcare professional communication (DHPC) was recommended.

In addition the PRAC imposed a post-authorisation safety study in order to better characterise the relative risk of thromboembolic events due to chlormadinone compared to the levonorgestrel-containing medicinal products.

Benefit –risk balance

Having considered all the above, the PRAC concluded that the benefit-risk balance of the medicinal products Evra, Ioa and Zoely in the indication of contraception remains favourable, subject to the inclusion of the restrictions, warnings and other changes to the product information agreed. In addition the marketing authorisation holders of chlormadinone should perform a post-authorisation safety study.

Grounds for the variation to the terms of the marketing authorisations

Whereas

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC for the combined hormonal contraceptives containing medicinal products.
- The PRAC reviewed all available data from clinical studies, pharmacoepidemiological studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holders (MAHs) in writing and at oral explanations, on the efficacy and safety of the combined hormonal contraceptive containing medicinal products, in particular with regards to the risk of thromboembolism. The PRAC confirmed the known risk of thromboembolism of combined hormonal contraceptive containing medicinal products, and recommended clear labelling of symptoms of thromboembolic events, as well as the risk factors for thromboembolic events.
- The PRAC considered that in view of the currently available safety data, the benefit-risk balance of combined hormonal contraceptives is favourable, subject to restrictions, warnings and other changes to the product information. In particular, these medicinal products should be contraindicated in patients with multiple risk factors (overweight, smoking, hypertension, increasing age etc.), in patients after major surgery with prolonged immobilisation and patients with history or hereditary predisposition of venous thrombosis. Further changes to the product information will contribute to better inform the healthcare professionals and women on the risk of thromboembolism.
- The PRAC is of the opinion that the benefits of combined hormonal contraceptive containing medicinal products continue to outweigh the risks in the indication of contraception.
- The PRAC considered that further data are required for the combined hormonal contraceptives containing chlormadinone and imposed the conduct of a post authorisation safety study (PASS) to evaluate the relative risk of thromboembolic events due to these products compared to the ones containing levonorgestrel.

The PRAC, as a consequence, concluded that the benefit-risk balance of the medicinal products Evra, Ioa and Zoely in the indication of contraception remains favourable, subject to the agreed conditions, restrictions, warnings, other changes to the product information and additional risk minimisation measures.

2 – Detailed explanation for the differences from the PRAC recommendation

Having reviewed the PRAC recommendation, the CHMP agreed with the overall scientific conclusions and grounds for recommendation. However, the CHMP considered that the section on Fertility, pregnancy and lactation of the SmPC should be amended to reflect the increased risk of VTE in the post-partum period, to ensure consistency with the warning section of the SmPC.

The following sentence was therefore inserted in the Pregnancy section of the SmPC:

"The increased risk of VTE during the postpartum period should be considered when re-starting [invented name] (see section 4.2 and 4.4)."

No further amendments were considered necessary.

CHMP opinion

The CHMP, having considered the PRAC recommendation dated 10 October 2013 pursuant to Article 107k(3) of Directive 2001/83/EC, is of the opinion that the marketing authorisations for Evra, Ioa and Zoely should be varied. The revised Summary of Product Characteristics (SmPC) and Package Leaflet (PL) are set out in the respective annexes I and IIIB for Evra, Ioa and Zoely.

Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-31/1356

Combined hormonal contraceptives (CHCs) containing medicinal products

The following CHMP Member supports the divergent position appended to the PRAC recommendation on combined hormonal contraceptives containing medicinal products dated 10 October 2013, as stated below:

CHMP members expressing a divergent position:

Jens Heisterberg (DK)	21 November 2013	Signature: .....
Jacqueline Genoux-Hames (LU)	21 November 2013	Signature: .....
John Joseph Borg (MT)	21 November 2013	Signature: .....
Pierre Demolis (FR)	21 November 2013	Signature: .....
Harald Enzmann (DE)	21 November 2013	Signature: .....
Jan Mueller-Berghaus (Co-opted)	21 November 2013	Signature: .....
Jean-Louis Robert (Co-opted)	21 November 2013	Signature: .....

<u>Divergent statement from PRAC Members</u>

The undersigned member of PRAC did not agree with the PRAC's opinion recommending that the Marketing Authorisation of combined hormonal contraceptives containing chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin or norgestimate should varied as stated by the PRAC.

These members are in full agreement with the scientific assessment made by the PRAC and based on the Rapporteur and co-rapporteur reports:

- They share the concerns over the risks of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) associated with those products.
- They agree with the well demonstrated increased risk of VTE observed with all the CHCs and the differences of risk between these contraceptives mainly driven by the type of progestogens.
- They agree with the range of risk as stated by the PRAC and compared to levonorgestrel containing CHC.

- They support the concern during the first ever year of use when the risk is highest and when restarting after a CHC-free interval of at least 4 weeks and for women with risk factors.

- They agree that there is currently no reliable evidence that newer CHCs have any higher beneficial effect or difference in tolerability

The reasons for this divergent opinion rely on the regulatory actions to take forward, focused on the wording of the section 4.1 Therapeutic indications of the SmPC and were as follows:

- The well documented differences in VTE incidence rates among users of different types of CHCs

- The lowest VTE risk is with products containing levonorgestrel, noresthisterone or norgestimate. In spite of previous reviews of benefits and risks of CHCs that have been conducted by European Member States during the past years as well as the CPMP position statement in 2001 together with a warning on VTE risk already being included in section 4.4 Special warnings and precautions for use and section 4.8 Undesirable effects of these products, VTE events of concern (number and seriousness) in the EU still persist.

Taking all these aspects into account, these members considered that there is a need for a clear recommendation in section 4.1 Therapeutic Indications for a targeted population "first ever users or women with an increased baseline risk of VTE".

For these women, these members were in favour of implementing in the "Indication" section of chlormadinone, desogestrel, dienogest, drospirenone, gestodene, nomegestrol, (those with a higher or a yet not sufficiently evaluated VTE risk) a recommendation to prescribe a CHC with a documented low VTE risk (levonorgestrel or noresthisterone or norgestimate containing product) with the aim of reducing the number of VTE events among CHC users, in particular in first ever users or women with an increased baseline risk of VTE.