Annex II

Scientific conclusions

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Ethinylestradiol is a synthetic estrogen while dienogest is a nortestosterone derivative which uniquely contains a cyanomethyl group at position 17α. Dienogest shows antiandrogenic properties, 10-30 fold lower affinity to progesterone receptor *in vitro* as compared to other synthetic progestogens. Dienogest does not have significant androgen, mineralocorticoid or glucocorticoid effects *in vivo*. The contraceptive effect of this combination is based on the interaction of various effects, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. Combined oral contraceptives (COCs) are thought to improve acne by several mechanisms.

At the time of triggering the referral, the UK considered that the benefit-risk analysis for the acne indication was not favourable based on insufficient data on the efficacy of the combination in the acne indication, an unacceptable safety profile, in particular regarding to the risk of venous thromboembolic events (VTE) and the fact that the target population covered by the abovementioned indication is broad and would unnecessarily expose women to a treatment with limited efficacy and to a potential higher risk of VTE when alternative and safer options for the treatment of acne are available.

In view of the above and the necessity to take an action at EU level, UK considered that it was in the interest of the Union to refer the matter to the CHMP and requested on the 18 February 2016, that it give its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products in the abovementioned indication should be maintained, varied, suspended, or revoked in relation to the below indication:

“Treatment of acne with moderate severity in women without contraindications for oral contraceptives and in whom topical treatment was ineffective”.

Overall summary of the scientific evaluation

When considering existing data in support of the efficacy of dienogest/ethinylestradiol, the CHMP concluded that overall there is sufficient evidence in support of the use of this combination in the acne indication. The phase III clinical studies showed that predominantly moderate acne vulgaris dominated in the studies. This is in line with the current treatment guidelines which state that combined oral contraceptives (COCs) are not indicated in mild acne, but are considered as treatment alternatives in females with moderate to severe acne.

The available safety data confirmed that the adverse event (AE) profile of DNG/EE and the comparator products in the phase III trials is very similar, with none of the safety parameters raising any concerns. The risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) is of particular importance as to date there is insufficient data to clearly determine the relative risk for thromboembolic events compared to other combined hormonal contraceptives containing other progestogens. However, the CHMP noted that there were no cases of VTE in the phase III studies and the safety data provided by MAHs does not raise any new safety concern. Oral contraceptives may also affect bone metabolism in adolescents, although this effect is likely reversible after discontinuation of treatment.

Considering the nature of the disorder, the observed benefits and the relative risks compared to available treatment alternatives and guideline recommendations, local therapies or oral antibiotic treatment should be tried first before resorting to a COC. Therefore, the benefit-risk relationship of DNG/EE is considered favourable for a second-line treatment of women with moderate acne. The CHMP also noted that in order to avoid unnecessarily exposing women to a treatment with a potential higher risk of VTE when alternative and safer options for the treatment of acne are available that the indication should be restricted to women who elect contraception, and that a conscious and well-considered decision needs to be made when choosing this COC.

In view of the most prominent effect on acne seen after 6 months of treatment, paired with the still to be quantified risk of VTE, women should be assessed 3-6 months after initiating treatment and periodically thereafter to review the need for continuation of treatment.

In view of the above, the CHMP concluded that the benefit-risk balance of dienogest/ethinylestradiol containing products indicated in acne is favourable subject to changes to the product information as described above.

Grounds for CHMP opinion

Whereas

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for medicines containing dienogest (DNG) 2 mg and ethinylestradiol (EE) 0.03 mg for moderately severe acne in women in whom topical treatment was ineffective.
- The CHMP considered the totality of the available clinical studies, published literature and post-marketing experience, including responses from marketing authorisation holders (MAHs) on the efficacy of DNG/EE in the treatment of acne, and on the safety of these medicines, in particular regarding the risk of venous thromboembolic events (VTE) and arterial thromboembolic events (ATE).
- The CHMP considered that the efficacy of medicines containing dienogest 2 mg and ethinylestradiol 0.03 mg in the treatment of moderately severe acne in women in whom topical treatment or oral antibiotic was ineffective is well supported by phase III clinical trial data and further supported by a Cochrane review of combined oral contraceptive pills for treatment of acne.
- The CHMP noted that the risk of VTE with dienogest containing combined hormonal contraceptive is not yet fully characterised. It is not known if the risk of VTE with DNG/EE is better or worse than that of the combined oral contraceptives containing levonorgestrel (5-7 per 10,000 women), etonorgestrel (6-12 per 10,000 women) or drospirenone (9-12 per 10,000 women as compared to 2 out of 10,000 women who do not use a combined hormonal contraceptive). However, the CHMP noted that there were no cases of VTE in the phase III studies and the safety data provided by MAHs does not raise any new safety concern.
- The CHMP also noted that the initial acne indication was too broad and would unnecessarily expose women to a treatment with a potential higher risk of VTE when alternative and safer options for the treatment of acne are available. The CHMP therefore agreed that the indication should be restricted to women who elect to use an oral contraceptive, and that a conscious and well-considered decision needs to be made when choosing this COC.
- The CHMP agreed that patients treated for acne should be assessed 3-6 months after starting treatment and periodically thereafter. This conclusion was reached considering that treatment would be necessary for at least 3 months for an effect to be seen, with the most prominent effect on acne seen after 6 months of treatment (as supported by the results of both phase III studies), and that in view of the still to be quantified risk of VTE, women should be assessed periodically to review the need for continuation of treatment.
- The CHMP is of the opinion that the benefits of dienogest/ethinylestradiol containing medicinal products continue to outweigh the risks in the second-line treatment of moderate acne in women who elect to use an oral contraceptive, provided that the medicinal products are only used after suitable topical therapies or oral antibiotic treatments have failed.

CHMP opinion

The CHMP, as a consequence, considers that the benefit-risk balance of dienogest/ethinylestradiol containing medicinal products indicated in acne remains favourable subject to the amendments to the product information described above.

Therefore the CHMP recommends the variation to the terms of the marketing authorisations for dienogest/ethinylestradiol containing medicinal products indicated in acne.