NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by the UK:

Product(s)	Dienogest/Ethinylestradiol containing products indicated in acne
Active substance(s)	Dienogest / Ethinylestradiol
Pharmaceutical form(s)	Film-coated tablets
Strength(s)	2 mg/0.03 mg
Route of administration(s)	Oral
Applicants/Marketing Authorisation Holder(s)	Various

Background

Dienogest 2mg/ethinylestradiol 0.03mg (Valette and associated names film-coated tablets) was originally approved via the Mutual Recognition Procedure with Germany as Reference Member State and AT, BE, DK, EL, ES, FI, FR, IE, IS, IT, LU, NL, NO, PT, SE as Concerned Member States.

The first marketing authorisation for Valette® (21 film-coated tablets) was apparently granted in Germany in 1995. Valette® (21 film-coated tablets) is authorised for oral contraception and for the treatment of moderate acne vulgaris. A number of generic applications have since been approved in the EU.

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 European Reference Product and related generics contained the following indication in addition to the use for oral contraception.

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

The UK considers that the benefit-risk analysis for the above indication in acne is not favourable for 0.03 mg Ethinylestradiol / 2 mg Dienogest products. Re-evaluation of the benefit risk balance in this indication is requested.

The evidence on efficacy and safety of this combination pertinent to the indication of acne is as below.

Efficacy: There is a single double-blind, randomized, parallel group study in support of the proposed indication of the treatment for Ethinylestradiol / Dienogest. The primary objective was to demonstrate the non-inferiority of ethinyl estradiol/ dienogest (EE2/DNG) in comparison to triphasic ethinyl estradiol/ norgestimate (EE2/NGM) in the treatment of mild to moderate acne. A total of 1040 subjects were randomized for 6 cycles of 28 days treatment. The primary endpoints in this study were the relative change in inflammatory lesion count in percent, relative change in total lesion count in percent and the proportion of patients who showed improvement of their facial acne according to the investigator's global assessment. The results showed that the mean relative change in total lesion count from randomization to Cycle 6 was -58.3% for the EE2/DNG treatment in comparison to -57.2% for the EE2/NGM treatment (Per-protocol sample - PPS). The mean relative change in inflammatory lesion count from randomization to Cycle 6 was -66.0% for the EE2/DNG treatment as compared to -65.4% on the mean for the EE2/NGM treatment (PPS). The proportion of patients who showed improvement of their facial acne according to the investigator's global assessment was 96.9% in the EE2/DNG group and 96.1% in the EE2/NGM group (PPS).

However there are a number of short-comings with the above study which preclude a conclusion of adequate evidence of efficacy. It is not clear if the active comparator used in the study is indicated for the treatment of acne and the basis (efficacy data supporting its use in acne) for its approval. Therefore demonstrating non-inferiority of EE2/DNG treatment in

comparison to EE2/NGM for the proposed indication is not appropriate as the choice of the active comparator is not fully justified. The criteria used for determining the severity of acne and the proportion of subjects with moderate acne (target indication) at baseline are not clear. The total number of lesion count/inflammatory lesions at base line is also unclear. More importantly, the assay sensitivity of the study and the proposed non-inferiority margin is not justified. The reported analyses do not provide results for the ITT population. In addition, without a comparison to placebo treatment arm, the efficacy of Ethinylestradiol / Dienogest cannot be inferred, as there is a high rate of spontaneous remission and exacerbations in acne.

Based on the above considerations, the conclusion of non-inferiority leading to demonstration of adequate efficacy cannot be accepted.

Safety:
In the phase III-study used to demonstrate the efficacy and safety of Ethinylestradiol / Dienogest for the acne indication. The three most frequently reported AEs were nausea (in 8.9% of the patients), upper respiratory infections (8.0%), and headache (7.9%). Four serious adverse events occurred in four patients (0.8%) of the EE2/DNG group these included degenerated uterine fibroids, psychic depression and Schizophrenia reaction. There was no incidence of venous thromboembolic events (VTE).

Venous thromboembolic events (VTE) and arterial thromboembolic events (ATE) are considered to be serious although they occur rarely therefore it is crucial that an appropriate estimate of this risk made particularly in the context of use in acne. The epidemiological data on the risk of VTE with dienogest-containing combined hormonal contraceptive is still not conclusive. It is not known if the risk of VTE with (EE2/DNG) is better or worse than the combined oral contraceptives containing levonorgestrel (5-7 per 10,000 women), etonorgestrel (6-12 per 10,000 women) and drospirenone (9-12 per 10,000 women as compared to 2 out of 10,000 women who do not use a combined hormonal contraceptive).

Dienogest/ethinylestradiol containing contraceptives were considered as part of a referral procedure under Article 31 on combined hormonal contraceptives (CHCs) and it was concluded that the available data were insufficient to characterise the risk of VTE with dienogest/ethinylestradiol. Since the finalisation of the Article 31 referral for CHCs, no further data or analysis was provided to further characterise this risk.

Given that the risk of VTE with ethinylestradiol/dienogest is unknown and also taking in to consideration the lack of adequate evidence on the efficacy, the UK considers that the benefit risk balance for the use of Ethinylestradiol 0.03 mg / Dienogest 2 mg is negative in the abovementioned indication.

Indication: The current indication in acne for Ethinylestradiol 0.03 mg / Dienogest 2 mg is - "*Acne with moderate severity in women without contraindications for oral contraceptives and in whom topical treatment was ineffective*". The target population covered by this broad indication is considered not appropriate in view of the limited efficacy and the potential adverse events of this combination. Women not seeking contraception may therefore be unnecessarily exposed to a potential higher risk of VTE when alternative and safer options for the treatment of acne are available.

Issues to be considered
The benefit risk of Dienogest / Ethinylestradiol for the indication "Acne with moderate severity in women without contraindications for oral contraceptives and in whom topical treatment was ineffective" is considered to be negative as:

- There is insufficient data on the efficacy of Dienogest/Ethinylestradiol for the abovementioned indication.

- The safety profile is not acceptable for the abovementioned indication, in particular regarding to the risk of venous thromboembolic events (VTE). This risk is not sufficiently characterised and would expose the women to unacceptable risk in light of the limited benefit of the indication.

- 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 considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives 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.

Signed Date 18 February 2016