Annex II

Scientific conclusions and grounds for refusal presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Ethinylestradiol-Drospirenone 24+4 and associated names (see annex I)

Ethinylestradiol-Drospirenone 24+4 is a combined oral contraceptive (COC) and contains ethinylestradiol 20 µg and the progestogen drospirenone 3 mg (EE/DRSP).

The Marketing Authorisation Holder (MAH), Bayer B.V. submitted a type II variation via mutual recognition procedure for Ethinylestradiol-Drospirenone 24+4 and associated names (NL/H/1269, 1270/01/II/006) on 26 January 2009, to request an extension of the indication to include:

"*Oral contraception for women with moderate acne vulgaris. This treatment does not exempt patients from specific acne treatment if necessary.*"

in section 4.1 "Therapeutic Indications" of the Summary of Product Characteristics (SmPC).

The efficacy results in the treatment of moderate acne derive from two placebo-controlled studies which are included in section 5.1 "Pharmacodynamic data" of the SmPC.

On 28 June 2011 and 29 June 2011 Italy and Sweden respectively, triggered a referral under Article 6(12) of Commission Regulation EC No 1084/2003. The CHMP was requested to give its opinion on whether the overall risk-benefit profile for Ethinylestradiol-Drospirenone 24+4 in the proposed indication was considered acceptable, particularly in light of the known greater risk of venous thromboembolic events (VTE) for DRSP-COCs in comparison with levonorgestrel (LNG)-COCs, and initiated the procedure in July 2011.

With the submission of the responses to the CHMP list of questions, the MAH changed the request for the indication and reverted to the indication as follows:

"*Treatment of moderate acne vulgaris only in women seeking oral contraception".*

The CHMP considered all the available data in view of the latter wording for the indication applied.

Efficacy

Acne is a skin disorder of the sebaceous follicles that presents with lesions that are either *inflamed* (i.e. papules, pustules and nodules) or *non-inflamed* (i.e. open- or closed comedones).

At least four patho-physiologic events take place within acne-infected hair follicles: i) androgen-mediated stimulation of sebaceous gland activity, ii) abnormal keratinisation leading to follicular plugging (comedo forming), iii) proliferation of the bacterium *Proprioni-bacterium acnes* (*P. acnes*) within the follicle, iv) inflammation.

Acne affects more than 50% of teenagers but frequently continues into adulthood. The mean age at presentation for treatment is 24 years, with 10% of treatment visits taking place when patients are between the ages of 35 and 44 years. The social, psychological, and emotional impairment that can result from acne has been reported to be similar to that associated with epilepsy, asthma, diabetes, and arthritis. Scarring can lead to lifelong problems in regard to self-esteem.

The classification of acne severity is from mild, moderate, moderately severe to severe depending on the presence of the lesions.

In support of this indication, two (A25083 and A25152) multicenter, double blind, randomised, placebo controlled studies were performed to evaluate the efficacy and safety of EE/DRSP in women with moderate acne vulgaris.

The overall efficacy assessment of EE/DRSP as a treatment for moderate acne vulgaris in reproductive age women observed during studies A25083 and A25152 demonstrates statistically significant responses to treatment with EE/DRSP as compared to placebo in all four primary

efficacy variables (inflammatory lesion, non-inflammatory lesion, and total lesion counts, and women with a 'clear' or 'almost clear' rating on the ISGA scale) and the majority of secondary efficacy variables (papules, pustules, closed and open comedones). The population included in the studies is considered representative of the respective target population for the treatment of moderate acne vulgaris.

After six months of treatment, in comparison with placebo, EE/DRSP showed a statistically and clinically significant reduction of 15.6% (49.3% versus 33.7%) in inflammatory lesions, 18.5% (40.6% versus 22.1%) in non-inflammatory lesions, and 16.5% (44.6% versus 28.1%) in total lesion counts. In addition, a higher percentage of subjects, 11.8% (18.6% versus 6.8%), showed a 'clear' or 'almost clear' rating on the Investigator's Static Global Assessment (ISGA) scale. As mentioned above, these results are reflected in the pharmacodynamic data's section of the product information for EE/DRSP- COCs.

Safety

The safety profile of EE/DRSP – COCs in the approved indication is well known. The most serious risks associated with its treatment are venous thromboembolic events (VTEs) and breast cancer:

Venous thromboembolic events (VTEs)

With regard to the VTE risk associated with EE/DRSP-COCs, the EURAS study (European led study) could not exclude a small difference in VTE risk between drospirenone and other combined OCs. The magnitude of this relative risk is similar to that found in previous studies of desogestrel/gestodene OCs when compared with LNG-OCs. This was corroborated by case-control studies that showed consistent results with a 2 to 3-fold greater risk for drospirenone versus LNG-containing OCs.

The most recent review by the Pharmacovigilance Working Party (PhVWP) concluded in January 2012, confirmed that DRSP-containing OCs are associated with a higher VTE risk than levonorgestrel-containing COCs and that the risk may be similar to that for desogestrel/gestodene-containing COCs.

This is an important factor which needs to be considered when selecting an oral contraceptive and may preclude EE/DRSP-COCs to be regarded as a first choice for contraception, in clinical practice.

Breast cancer

With regard to breast cancer risk, the largest meta-analysis to date, including 53297 women with breast cancer and 100239 controls, showed that current use of combined OCs was associated with a relative risk (RR) of 1.24 (95 % confidence interval 1.15–1.33). Moreover, when data were analysed by age at first use, women who started OC use before age 20 had a higher risk of breast cancer than those starting later, RR = 1.22 (95 % confidence interval 1.17–1.26; *Lancet 1996*).

Overall, the safety profile of EE/DRSP oral contraceptives is known from its use as oral contraception and associated with rare but serious adverse events (i.e. VTE and breast cancer). The VTE associated risk is higher for EE/DRSP oral contraceptives when compared to other combined oral contraceptives.

Risk Minimisation Measures

The MAH submitted a risk minimisation program to ensure the safe use of EE/DRSP COCs and to limit possible off-label use following authorisation of the applied indication.

The specific content of the proposed educational program was to be agreed with the national competent authorities following the authorisation of the combined indication. General tools (e.g. lectures, conferences, symposia) targeting health care providers were proposed as educational material for prescribers by emphasising on the benefit/risk of EE/DRSP use in targeted population

and discourage off-label use as well as to highlight to the patients that treatment of moderate acne with EE/DRSP is limited to patients who indeed require hormonal contraception.

In addition, and in order to monitor the effectiveness of the educational program with the consequent monitoring of the EE/DRSP-COCs prescribing practices in Europe, two drug utilization studies were proposed. The MAH also committed to further improve and expand the educational program if the prescribing rate for the treatment of moderate acne in women not seeking contraception resulted higher than 10% in both drug utilization studies.

The CHMP considered the MAH proposed measures for risk minimisation not sufficient to ensure the safe and effective use of EE/DRSP in the specific applied clinical situation. The prescription guide is expected to have a little impact on adherence to and compliance with the product information.

Overall benefit-risk assessment

The overall efficacy of EE/DRSP as a treatment for moderate acne vulgaris in reproductive age women was shown in the two placebo-controlled A25083 and A25152 studies. Statistically significant responses to treatment with EE/DRSP as compared to placebo was seen in all four primary efficacy variables (inflammatory lesion, non-inflammatory lesion, and total lesion counts, and women with a 'clear' or 'almost clear' rating on the ISGA scale). The mean difference observed in total lesion count reduction is of 16% between EE/DRSP and placebo.

The safety profile of the EE/DRSP is known from its use as oral contraception. The treatment with EE/DRSP is associated with venous thromboembolic events (VTE) and with breast cancer risks. In this regard, a recent safety review performed in January 2012 by the Pharmacovigilance working party, confirmed that DRSP-containing OCs are associated with a higher VTE risk than levonorgestrel-containing OCs and that the risk may be similar to that for desogestrel/gestodene-containing OCs. This is an important factor when prescribing an oral contraceptive and may preclude EE/DRSP-COCs to be regarded as a first choice for contraception, in clinical practice.

With regard to breast cancer risk, published data showed that the current use of combined OCs is associated with a relative risk (RR) of 1.24 (95 % confidence interval 1.15–1.33). Moreover, women who started OC use before age 20 had a higher risk of breast cancer than those starting later, RR = 1.22 (95 % confidence interval 1.17–1.26; *Lancet 1996*).

Overall, the safety profile of EE/DRSP oral contraceptives is known and associated with serious adverse events (i.e. VTE and breast cancer). The VTE associated risk is higher for EE/DRSP oral contraceptives when compared to other combined oral contraceptives.

Considering all the above and the fact that acne is a very common condition in young women, the Committee raised concerns that a beneficial effect noted by the patient from use of EE/DRSP would reduce the motivation to stop the intake when the need for contraception ceases and, therefore, it would not be possible to ensure that the use of the medicinal product would be limited to the treatment of moderate acne vulgaris only in women seeking oral contraception. This is of concern as the risk of venous thromboembolism for drospirenone-containing OCs is higher (approximately 2-fold) than for levonorgestrel-containing OCs.

The CHMP considered the MAH proposed measures for risk minimisation to ensure the safe use of EE/DRSP COCs and to limit possible off-label use following authorisation of the applied indication. Namely, the educational program and the drug utilization studies proposed to monitor the effectiveness of the measures. These were regarded as not sufficient to ensure the safe and effective use of EE/DRSP in the specific clinical situation. The prescription guide is expected to have a little impact on adherence to and compliance with the product information.

Thus, the potential to restrict the duration of treatment by the proposed risk minimisation program is not considered realistic or sufficiently effective. In addition, the dual need for treatment of acne while the patient will also need oral contraception will exist at time of prescribing. Indeed, the

prescriber will verify the need for a treatment for acne at the start of the prescribing period. The MAH has not convincingly shown how this can be ensured during treatment. Furthermore the MAH failed to show that once the need for oral contraception seizes to exist, the patients will be switched to other acne treatments. Therefore, it remains of concern the potential for unnecessary exposure to EE/DRSP for prolonged periods for the acne indication alone and that the proposed activities for risk minimisation are insufficient to ensure use of EE/DRSP for the acne indication only by women seeking oral contraception.

Based on the above, the Committee is of the opinion that the inclusion of treatment of acne vulgaris in the indication may increase unnecessarily the use of EE/DRSP relatively to safer combined oral contraceptive and that minimisation measures that could ensure an acceptable risk level in this clinical situation could not be identified.

Therefore, the CHMP concludes that the variation application does not satisfy the criteria for authorisation and recommends the refusal of the variation to the terms of the Marketing Authorisation for all medicinal product(s) referred to in Annex I.

Grounds for refusal

Whereas

- The Committee considered the procedure under Article 6(12) of Commission Regulation (EC) no 1084/2003, for Ethinylestradiol-Drospirenone 24+4 and associated names initiated by Italy and Sweden. These Member States considered the approval of the variation to constitute a serious risk for public health on the basis that the overall risk-benefit profile for Ethinylestradiol-Drospirenone 24+4 in the proposed indication was considered not acceptable in light of:

  a) the known greater risk of venous thromboembolic events (VTE) for DRSP-COCs in comparison with levonorgestrel (LNG)-COCs;

  b) the potential use of the product for women who are not comprised in the target population.

- The Committee considered all the available data submitted from efficacy and safety.
- The Committee noted the overall efficacy of EE/DRSP as a treatment for moderate acne vulgaris in reproductive age women was shown in two placebo-controlled studies. The CHMP recognised the efficacy in the overall lesion count reduction.
- The Committee considered the known safety profile of EE/DRSP in particular the higher risk associated with VTE in comparison to other available OCs.
- The Committee found merit on the concerns raised by the Member States regarding the continuation of use of EE/DRSP in the treatment of moderate acne when contraception is no longer needed for which the benefit/risk balance is not acceptable considering the risk of rare but serious adverse events balanced against the limited clinical benefits. The Committee considered that the risk minimisation measures proposed would not ensure that the use of the product would be limited to treatment of moderate acne only in women seeking oral contraception and could not identify other risk minimisation measures which would reduce such risk. Therefore the Committee concluded that the variation application should be refused. The CHMP noted that other treatment options are available for the treatment of acne alone.

Consequently, the CHMP concluded in accordance with Article 32 (4) of Directive 2001/83/EC that the variation application does not satisfy the criteria for authorisation and recommends the refusal

of the variation to the terms of the Marketing Authorisation for Ethinylestradiol-Drospirenone 24+4 and associated names (see Annex I).