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Patient Health Protection
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Referral assessment report

Ethinylestradiol-Drospirenone 24+4 and associated names

INN: ethinylestradiol/drospirenone

Procedure number: EMEA/H/A-6(12)/1313

Referral under Article 6(12) of Commission Regulation EC No 1084/2003

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

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1. Background information on the procedure

1.1. Referral of the matter to the CHMP

On 28 June 2011 and 29 June 2011, AIFA, Italy and MPA, Sweden, triggered a referral under Article 6(12) of Commission Regulation EC No 1084/2003. 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.

Therefore, 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 above concerns.

The procedure described in Article 32 of Directive 2001/83/EC, as amended, was applicable.

2. Scientific discussion

2.1. Introduction

Ethinylestradiol-Drospirenone is a combined oral contraceptive indicated for *"Oral contraception",* Ethinylestradiol-Drospirenone 24+4 contains ethinylestradiol (EE) 20 µg and the progestogen drospirenone (DRSP) 3 mg (EE/DRSP).

The MAH Bayer B.V. submitted a type II variation via MRP for Ethinylestradiol-Drospirenone 24+4 and associated names on
26 January 2009 to add an indication. The additional new indication proposal (in addition to the established indication in oral contraception) submitted in section 4.1 of the Summary of Product Characteristics (SmPC) during the variation procedure which was referred to the CHMP was:

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

The efficacy results in the treatment of moderate acne from two placebo-controlled studies are currently already included in section 5.1 of the SmPC.

The Reference Member State (RMS) is The Netherlands and the Concerned Member States (CMS) are Austria, Bulgaria, Cyprus, Czech Republic, Denmark, Germany, Greece, Finland, France, Iceland, Italy, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

The RMS concluded that the amount of clinical evidence in support of the treatment of moderate acne vulgaris, which included two placebo-controlled studies currently described in section 5.1 of the SmPC, is considered sufficiently robust for inclusion of this indication in section 4.1 of the SmPC. However Italy and Sweden 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.

Based on the above, these Member States on 28 June 2011(Italy) and 29 June 2011 (Swedeen) triggered a referral under Article 6(12) of Commission Regulation EC No 1084/2003 requesting the CHMP to give its opinion on whether the overall risk-benefit profile for Ethinylestradiol-Drospirenone 24+4 in the proposed indication was considered acceptable. The procedure was initiated in July 2011.

With the submission of the responses to the CHMP LoQs, the MAH changed the request for the indication and reverted to the indication

"*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.

2.2. Clinical 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.

Although acne is one of the most common skin disorders, its pathophysiology is poorly understood. The cause of the hyperproliferation of keratinocytes and the abnormalities of differentiation and desquamation are unknown. It is likely that hyper-responsiveness to the stimulation of sebocytes and follicular keratinocytes by androgens leads to the hyperplasia of the sebaceous glands and the seborrhoea that characterise acne.

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 as follows:

***Mild*:**

Comedones (non-inflammatory lesions) are the main lesions. Papules and pustules may be present but are small and few in number (generally <10).

***Moderate*:**

Moderate numbers of papules and pustules (10–40) and comedones (10–40) are present. Mild disease of the trunk may also be present.

Moderately severe:

Numerous papules and pustules are present (40–100), usually with many comedones (40–100) and occasional larger, deeper nodular inflamed lesions (up to 5). Widespread affected areas usually involve the face, chest, and back.

***Severe*:**

Nodulocystic acne and acne conglobata with many large, painful nodular or pustular lesions are present, along with many smaller papules, pustules, and comedones.

There is no consensus as to the most appropriate approach to the management of acne.

Treatment options currently available include topical retinoids (derivatives of vitamin A), topical antimicrobials (benzoyl peroxide with or without clindamycin, erythromycin, azelaic acid), oral treatment with antibiotics (tetracycline, doxycycline, minocycline, erythromycine), oral isotretinoin and combined oral contraceptives.

2.2.1. Main studies

Proof of the clinical efficacy of ethinylestradiol/drospirenon (EE/DRSP) in the treatment of moderate acne vulgaris is based on the data of 2 pivotal clinical phase III studies: A25083 and A25152 (table 1). The studies were identical with respect to their design and study course except for additional hormone measurements that were performed in a subgroup of 40 women in study A25083.

Table 1: Overview of clinical phase III studies of EE/DRSP in the treatment of moderate acne vulgaris

Study	Title/design	Total number of women by treatment group*	Treatment duration	Efficacy parameters
A25083 (US)	*moderate acne vulgaris* multicenter, double-blind, randomized, placebo-controlled	EE/DRSP: 229 Placebo: 227	6 cycles	Primary efficacy variable: percentage change from baseline in inflammatory lesion counts, non-inflammatory lesion counts, total lesion count, and percentage of subjects classified as '0' (clear skin) or '1' (almost clear skin) on the Investigator Static Global Assessment (ISGA) scale. Secondary efficacy variable: change from baseline in count of papules, pustules, nodules, open comedones, and closed comedones, and the percentage of women with improvement on the Investigator's Overall Improvement Rating and on the Subject's Overall Self-assessment Rating. Change from baseline to cycle 6 in the Ferryman-Gallwey hirsutism scale score for upper lip and chin.
A25152 (US)	*moderate acne vulgaris* multicenter, double-blind, randomized, placebo-controlled	EE/DRSP: 222 Placebo: 215	6 cycles	

* Note: the number of women refers to the amended FAS (a minimum of 40 lesions, i.e. at least 20 inflammatory lesions and at least 20 non-inflammatory lesions)

The design principles of the placebo-controlled studies were based on two published studies evaluating the combined oral contraceptives (OC) containing norgestimate/EE compared to placebo for the treatment of moderate acne (Redmond *et al*. 1997, Lucky *et al*. 1997). EU guidelines do not contain a requirement to conduct an active comparator controlled trial. The ICH E9 guideline indicates that a possible active comparator should be acceptable to the region for which the data are intended.

The MAH justified that the medicinal products approved for the treatment of acne on a national level are not authorised for this indication throughout the European Union. Therefore, no 'standard' could be identified as suitable comparator drug. Furthermore, other treatments like anti-infective agents or dermatological preparations were not considered acceptable as these are no hormonal products and cannot be used in the indication of oral contraception.

Both studies have a randomised and double blind study design fulfilling the design principles of clinical trials as mentioned in ICH E9. For the subsequent analysis the “intent-to-treat” principle was implemented by applying the LOCF approach for all subjects e.g. that for subjects who had no assessment under treatment the baseline assessment was carried forward as the endpoint resulting in a percent change of 0. Thus, the approach of a double-blind, placebo-controlled study design is justified.

In both studies A25083 and A25152, the same inclusion and exclusion criteria were used:

Inclusion criteria

- women between 14 and 45 years old, ≥ 1 year post-menarche, requesting treatment for moderate acne vulgaris,
- no contraindications for OC use who were in good general health, could be included.
- Women had to have a minimum of 40 lesions with at least 20 inflammatory lesions (papules or pustules), 20 non-inflammatory lesions (comedones), not more than 3 small inactive nodules and who would not be classified as grade 0, 1, or 2 on the Investigator Static Global Assessment (ISGA) scale [1].

Extra **exclusion** criteria ***specific for acne studies*** in addition to those also applied in the contraception studies:

- to guarantee stable baseline conditions, the following washout periods had to be observed before the initial acne lesion count:
  - three months free of contraceptive implants or hormonal contraceptive intra-uterine devices/systems
  - two months free of oral contraceptives
  - six months free of systemic isotretinoin or injectable contraception
  - eight weeks free of other systemic ethical anti-acne agents (e.g. antibiotics)
  - four weeks free of topical retinoids
  - two weeks free of other topical anti-acne agents (e.g. topical antibiotics, benzoyl peroxide)

[1] *ISGA scale: 0 = normal, clear skin with no evidence of acne vulgaris; 1 = skin is almost clear: few non-inflammatory lesions present, with rare noninflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red), no nodular lesions; 2 = few inflammatory lesions (papules or pustules), little inflammation, some comedones, no nodular lesions*

The methods of dermatological assessment, the study design and the primary efficacy variables were similar in both clinical studies.

1. Percentage change from baseline in inflammatory lesion count (papules, pustules, and nodules)
2. Percentage change from baseline in non-inflammatory lesion count (open and closed comedones)
3. Percentage change from baseline in total lesion count (comedones, papules, pustules, and nodules)
4. Percentage of women classified as '0' (clear skin) or '1'(almost clear skin) on the 6-point ISGA scale

The Table 2 below summarises the methods applied to evaluate the primary efficacy variables of studies A25083 and A25152 relevant to the use of EE/DRSP as a treatment of moderate acne vulgaris.

Table 2. Overview of methods to evaluate the primary efficacy parameters to support the indication of moderate acne vulgaris

1. Percentage change in inflammatory lesions (papules, pustules, and nodules)	Acne lesion counts covering the entire face (area bounded by the ears, the hairline, and lower margin of the mandibles) were conducted by the Dermatologist or trained designee at screening and each scheduled treatment visit. The nose was excluded when counting comedones. The person performing the acne lesion counts was not to be involved in collecting/documenting AEs or information about menses in order to keep the study blinded.
2. Percentage change in non-inflammatory lesions (open comedones and closed comedones)	
3. Percentage change in total lesions (inflammatory and non-inflammatory)	
4. Investigator Static Global Assessment (ISGA)	ISGA was obtained at screening and at each scheduled treatment visit. This evaluation of the overall status of each subject's acne was rated on a 6-point scale 0 = normal, clear skin with no evidence of acne vulgaris; 1 = skin is almost clear: few non-inflammatory lesions present, with rare non-inflamed papules (papules must be resolving and may be hyperpigmented, though not pink-red), no nodular lesions; 2 = few inflammatory lesions (papules or pustules), little inflammation, some comedones, no nodular lesions

The definition of the standards for evaluation of clinical response to acne treatment were addressed in methodological reviews (Lehmann *et al*. 2002, Del Rosso, 2006).

Lehmann and colleagues (2002) identified more than 25 methods of assessing acne severity and more than 19 methods of counting lesions. Based on the data reviewed they provided a list of methodological recommendations. The design and outcomes of studies A25083 and A25152 are in line with these recommendations. Del Rosso (2006) compared previous criteria used by other regulatory authorities for approval of anti-acne therapies with new methodologies such as the ISGA scale and suggested a global evaluation scale. In the two acne studies performed by the MAH efficacy was assessed using both new static global evaluation methodology and conventional lesion counts.

In summary, the study endpoints including percentage change from baseline in inflammatory lesion count (papules, pustules, and nodules), non-inflammatory lesion count (open and closed comedones), total lesion count, investigators' static assessment as well as a self-assessment rating by the patients, addressed both objective and subjective endpoints.

Secondary efficacy variables were the change from baseline in count of papules, pustules, nodules, open comedones, closed comedones.

1. Percentage of women classified as 'improved' according to the Investigator's Overall Improvement Rating (6-point scale: clear, excellent improvement, good improvement, moderate improvement, no improvement, and deterioration)
2. Percentage of women classifying themselves as 'improved' on the Subject's Overall Self-assessment Rating (5-point scale: excellent improvement, good improvement, fair improvement, no improvement, and worse).

A successful outcome for EE/DRSP in the treatment of moderate acne vulgaris was defined as the statistically significantly greater reductions in the percentage change from baseline to treatment endpoint in 2 of the 3 lesion counts (inflammatory, non-inflammatory or total lesion count) and a statistically significantly higher percentage of women classified as 'clear' or 'almost clear' on the ISGA scale at treatment endpoint.

Results

Overall, a total of 893 women were assigned i.e. 451 women in the EE/DRSP group and 442 in the placebo group. The majority of women reached treatment cycle 6 in both treatment groups (363 women in the EE/DRSP group and 336 women in the placebo group). There were 15 women in the EE/DRSP group and 7 women in the placebo group to whom study medication was dispensed but not administered. For 3 women in each group, no diary or medication usage data were available. All randomised women who were dispensed study medication were included in the analysis regardless of having any post-baseline data.

Patient Demographics

An analysis of demographic and baseline characteristics (including dermatological baseline findings, gynaecological, medical, surgery and medication history) revealed that the study populations included in the individual studies and treatment groups were very similar. Therefore, the pooled data across the studies A25083 and A25152 are considered representative of the overall study population.

Concomitant medication

The distribution of women who used concomitant medications during the treatment phase was comparable between the two treatment groups. Concomitant medications were taken in 55.9% in the EE/DRSP group and 54.3% in the placebo group. The most commonly used concomitant medications in the EE/DRSP and placebo groups, respectively were: ibuprofen (16.0% versus 12.7%), paracetamol combinations excluding psycholeptics (9.8% versus 10.4%), paracetamol (9.3% versus 6.6%), multivitamins, plain (4.9% versus 6.1%), amoxicillin (4.2% versus 2.5%), naproxen (3.5% versus 3.6%), salbutamol (2.4% versus 4.8%) and azithromycin (2.2% versus 3.4%).

Primary efficacy variable results

a. Inflammatory lesions

Comparison between treatment groups of mean percent change from baseline to endpoint in inflammatory lesion count showed that the EE/DRSP group had a statistically significantly larger decrease in inflammatory lesion count at endpoint compared with the placebo group (adjusted mean

difference –15.348%; p<0.0001). Endpoint was defined as visit 5 (i.e. days 17 to 24 of cycle 6), with missing values replaced by LOCF.

b. Non-inflammatory lesions

Comparison between the 2 treatment groups showed that the decreases were more pronounced in the EE/DRSP group compared with the placebo group during the treatment phase at all post-baseline visits except for the first treatment cycle.

c. Total lesion count

The mean total lesion count at baseline was comparable between the EE/DRSP and placebo groups. The results showed that the mean percent change from baseline to endpoint in the EE/DRSP group had a statistically significantly larger decrease in total lesion count at endpoint compared with the placebo group (adjusted mean difference –16.148%; p<0.0001).

d. Investigator static global assessment (ISGA)

The number and percentage of women with an ISGA rating of 'clear' or 'almost clear' in the EE/DRSP group greatly increased during the treatment phase over time compared with the placebo group (TT 21). Statistical analysis showed that the probability that the skin was 'clear' or 'almost clear' on the ISGA rating scale at endpoint was statistically significantly higher in the EE/DRSP treatment group (proportion=18.6%) compared with the placebo group (proportion=6.8%). The resulting odds ratio was 3.413 (CI: 2.146, 5.426; p<0.0001). Table 3 below gives an overview of the results of the primary efficacy endpoint:

Table 3: Overview of primary efficacy variable results – amended FAS (pooled data of studies A25083 and A25152)

Amended FAS EE/DRSP: N= 451 Placebo: N=442	**Percent Change from Baseline to Endpoint [3]**			**Odds Ratio at Endpoint [3], [4]**
	Inflammatory Lesions	**Non-inflammatory Lesions**	**Total Lesions**	**ISGA**
	EE/DRSP: n=450 Placebo: n=442	EE/DRSP: n=450 Placebo: n=442	EE/DRSP: n=450 Placebo: n=442	EE/DRSP: n=451 Placebo: n=442
EE/DRSP vs Placebo [1]	-15.348%	-18.091%	-16.148%	3.413
95% CI	-20.427%, -10.268%	-23.553%, -12.629%	-20.685%, -11.612%	2.146, 5.426
p-value	p<0.0001 [2]	p<0.0001 [2]	p<0.0001 [2]	p<0.0001

[1] difference in adjusted treatment means (i.e. EE/DRSP minus placebo)
[2] p-value from ANCOVA with terms treatment, protocol, pooled center within protocol, and baseline covariate.
[3] endpoint is cycle 6/visit 5 data with missing values replaced in accordance with the LOCF procedure
[4] p-value, odds ratio, and confidence limits computed from Cochran Mantel-Haenszel statistic stratified by pooled centre, since the logistic regression model did not converge.

There were statistically significant reductions in inflammatory lesion, non-inflammatory lesion, and total lesion counts over time within the EE/DRSP and placebo groups. However, the reductions in all the counts were greater in the EE/DRSP group compared with the placebo group. Women treated with placebo demonstrated statistically significant reductions from baseline, which may in part be due to some women at a given severity improving spontaneously due to the fluctuating clinical course of the disease. Increased attention to skin hygiene and avoidance of comedogenic preparations may also have contributed to the placebo response.

Secondary efficacy variable results

Statistically significantly reductions in the mean change from baseline to endpoint in the EE/DRSP group compared with the placebo group were also observed in the following secondary efficacy

variables of individual lesion counts: papules (adjusted mean difference –3.1; p=0.0001), pustules (adjusted mean difference –1.2; p=0.0124), open comedones (adjusted mean difference –3.0; p=0.0037), and closed comedones (adjusted mean difference –3.9; p=0.0001). The mean nodule count remained essentially constant throughout the study and was very low in both treatment groups. Since the aim of this study was to study moderate acne and not severe acne, there were too few nodules to make any conclusions.

Sub-population analysis

Subgroup analyses of the primary efficacy variables were performed in order to assess whether the claimed treatment effects were observed consistently throughout the overall study population. An efficacy analysis was performed for the following subgroups: age (14-22, 23-26, 27-30, 31-34, and 35-45 years), ethnic groups, baseline lesion count (40-60 lesions, and more than 60 lesions) and baseline ISGA rating (rating 2, 3, 4 and 5 at baseline). In summary, subgroup analyses by age, ethnic groups, baseline lesion counts and baseline ISGA rating were, in general, consistent with the analysis of primary variable results.

2.2.2. Conclusions and discussion on the efficacy results

The overall efficacy assessment of the OC 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 4 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 is considered representative of the respective target population for the treatment of moderate acne vulgaris (James, 2005).

The inclusion criteria applied for the study population are considered in line with the definitions for moderate and severe acne applied in medical literature.

The selection of primary end points chosen to evaluate efficacy of EE/DRSP in the treatment of moderate to severe acne vulgaris is considered adequate. Apart from lesion counts, the primary end point 'clear or almost clear' rating is considered a good addition to lesion count as it represents a very relevant clinical outcome from a patient point of view. Combining these endpoints contributes to the overall picture of the efficacy.

In summary, 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.

2.3. Clinical 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 (VTE)

With regard to the VTE risk associated with EE/DRSP, the EURAS study (European led study) could not exclude a small difference in VTE risk between drospirenone and other combined OCs. The interim report of the International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC[2]) study did not suggest a risk difference vs other COCs. Lidegaard and colleagues (2009), however, showed evidence that there is a higher risk for VTE with drospirenone containing OCs as compared with levonorgestrel (LNG)-containing OCs. The magnitude of this difference was uncertain. Furthermore, the two recent papers by Jick and colleagues (2007 and 2009) added important weight to the evidence of a difference in VTE risk between drospirenone - and LNG OCs. The magnitude of this relative risk is similar to that found in previous studies of desogestrel/gestodene OCs when compared with LNG-OCs. Thus, the two cohort/nested case-control studies in a claims database in the US and clinical database in the UK show 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.

Breast cancer

With regard to breast cancer risk, the largest meta-analysis to date, including 53,297 women with breast cancer and 100,239 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.

Other safety considerations

An important problem with a conditional acne indication in daily clinical routine is how and by whom the diagnosis of moderate acne will be made and who should take responsibility for the follow-up and continued benefit-risk balance of treating moderate acne with EE/DRSP. In a clinical setting - except among dermatologists - the grading of disease severity to diagnose moderate acne is not well established and it is not clear how “moderate acne” should be diagnosed. Surveys have reported that self-reporting of acne is unreliable for the assessment of the degree of the disease (Menon, C. *et al*., 2008). The association between clinical severity and psychological effects is not strong (Law MPM, *et al.,* 2009). Thus, also mild acne lesions may cause psychological distress in many women, leading to a request for treatment over prolonged periods of time.

Acne may be a long-standing inflammatory skin condition and a woman who needs treatment for acne is expected to request treatment for a long period of time. It is acknowledged that combined oral contraceptives (COCs) can improve acne in some women. However differences in effectiveness among different COCs have been described and it is not clear how EE/DRSP compares with alternatives therapies (other COCs or non-hormonal treatments). The risks associated with COCs should be taken into account. VTE risk related to EE/DRSP seems higher than the one associated to other COCs (those containing levonorgestrel) and 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.

[2] INAS-OC = International Active Surveillance Study of Women taking Oral Contraceptives. A prospective, controlled, non-interventional, long-term cohort study that follows a series of cohorts. The INAS-OC study started in 2005 and recruitment is completed. Interim reports have been and are being submitted to EU authorities at regular intervals.

It is questionable when the need for oral contraception would no longer be there whether the patient will discontinue OC use, particularly if an improvement may be observed. It is possible that women with acne receiving EE/DRSP keep taking this COC when contraception is no longer needed if they have the perception that the product improves acne. In such cases the VTE risk, acceptable for contraception purposes, could not be considered as acceptable for treating only acne

2.4. Risk Management Plan

The MAH accepted that the main indication of EE/DRSP remains oral contraception. To address the concerns that there might be an "off-label" use the MAH would commit to conduct a risk minimization program to ensure that the product is prescribed and used according to its labelled indications.

The proposed risk minimization plan would consist of the following elements:

1. A basic educational program to reduce potential off-label use with approval of the acne indication subject to agreement with the national competent authorities.

   The following general tools for health care providers (e.g., GPs, gynaecologists, dermatologists, pharmacists) are suggested to achieve the basic educational outreach objectives with emphasis on the risk/benefit of use and the of off-label use in women who do not require contraception: Lectures on risk/benefit at national conferences, symposia and workshops, medical educational slide kit, visual aid (prescription guide), product monograph, patient information card.

2. Two drug utilisation studies:

   a. New drug utilisation study to monitor the EE/DRSP prescribing practices in Europe and the effectiveness of the educational program

   b. Inclusion of respective questions on the reason for OC prescriptions into an INAS-like study to monitor the EE/DRSP off label prescribing practices in Europe and to assess a potential public health risk due to off-label use.

If the prescribing rate for treatment of acne in women who are not seeking contraception is greater than 10% in either drug utilisation study, the MAH would also commit to work with local health authorities and professional prescribing organisations to improve and expand the educational efforts.

The MAH proposed also a Post Authorisation Safety Study (PASS) study to compare risks of rare serious clinical outcomes in oral contraceptive users (e.g. cardio-vascular outcomes) with a special emphasis on EE/DRSP users to monitor EE/DRSP prescribing practices during typical clinical use and to assess the overall safety and efficacy of typical oral contraceptive use.

The CHMP, having considered the data submitted was of the opinion that the proposed risk minimisation activities were not able to reduce the risks to an acceptable level. A combined indication in the treatment of acne may lead to a preferential use of this COC in young women, which is of concern as the risk of venous thromboembolism for drospirenone-containing OCs is higher (approximately 2-fold) than for levonorgestrel-containing OCs. Furthermore, off-label use in women not seeking oral contraception is not likely to be prevented by a risk minimization program. This is of concern, especially when we consider that other products are available for the treatment of acne (e.g. topical antimicrobials).

Therefore, 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.

2.5. 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.

Divergent opinions of CHMP members have been expressed during the assessment of this variation to the terms of the marketing authorisation.

These divergent opinions were based on the considerations that a clinical relevant effect on acne versus placebo was shown; the placebo-controlled trials were designed according to the regulatory recommendations for placebo-controlled trials; the absence of active controlled studies is considered acceptable as no alternative treatment option within the class of COCs can be identified and no suitable comparator was available for clinical trials.

Even if the relative risk of VTE for drospirenone-containing OCs is higher than for levonorgestrel-containing OCs the absolute risk of VTE is still very low. This risk level is acceptable for women seeking OCs. This risk in healthy non-COC users of fertile age is about 10 cases per 100.000 women years, OCs in healthy women increase this risk to 20-40 cases per 100.000 treatment years of COC-use (RR= 2-4). In women with additional risk factors the absolute numbers are higher, but that applies to all COCs.

The target population for the acne indication was limited to a group that is prescribed an oral contraceptive. However, to address the concern that there might be off-label use the MAH was prepared to initiate a risk minimisation program with an educational program and two utilisation studies. If the prescribing rate for treatment of acne in women who are not seeking contraception is found greater than 10% in either drug utilisation study, the MAH would work with local health authorities and professional prescribing organisations to expand the educational efforts.

Other treatments in acne have their limitations, topical/oral retinoids are contra-indicated in women of childbearing age because of teratogenic risks and prolonged antibiotic therapy carries a risk of inducing resistance and could reduce efficacy of hormonal contraception.

The divergent positions are appended to this assessment report.

3. Overall conclusion

Having considered the overall submitted data provided by the MAHs in writing and in the oral explanation, the CHMP concluded:

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.

Appendix 1

Divergent positions dated 19 April 2012

Article 6(12) referral of Commission Regulation (EC) no 1084/2003, as amended

Procedure No: EMEA/H/A-6(12)/1313

Ethinylestradiol-Drospirenone 24+4 and associated names (INN: ethinylestradiol/drospirenone)

Divergent statement

Based on the presented clinical evidence in their totality, we are of the following opinion:

A clinical relevant effect on moderate acne versus placebo was shown; the placebo-controlled trials were designed according to the regulatory recommendations for placebo-controlled trials; the absence of active controlled studies is considered acceptable as no alternative treatment option within the class of COCs can be identified and no suitable comparator was available for clinical trials.

Even if the relative risk of VTE for drospirenone-containing OCs is higher than for levonorgestrel-containing OCs the absolute risk of VTE is still very low. This risk level is acceptable for women seeking OCs. This risk in healthy non-COC users of fertile age is about 10 cases per 100.000 women years, OCs in healthy women increase this risk to 20-40 cases per 100.000 treatment years of COC-use (RR= 2-4). In women with additional risk factors the absolute numbers are higher, but that applies to all COCs.

The target population for moderate acne indication was limited to a group that is prescribed an oral contraceptive. However, to address the concern that there might be off-label use the MAH was prepared to initiate a risk minimisation program with an educational program and two utilisation studies. If the prescribing rate for treatment of moderate acne in women who are not seeking contraception is found greater than 10% in either drug utilisation study, the MAH would work with local health authorities and professional prescribing organisations to expand the educational efforts.

Other treatments in moderate acne have their limitations, topical/oral retinoids are contra-indicated in women of childbearing age because of teratogenic risks and prolonged antibiotic therapy carries a risk of inducing resistance and could reduce efficacy of hormonal contraception.

CHMP members expressing a divergent opinion:

Robert James Hemmings (UK)	**19 April 2012**	**Signature: ……..**
Ian Hudson (UK)	19 April 2012	Signature: ……...

Irs Alar (EE)	19 April 2012	Signature: …….....
Beatriz Silva Lima (PT)	19 April 2012	Signature: …….....
Outi Mäki-Ikola (FI)	19 April 2012	Signature: …….....
Pieter Neels (BE)	19 April 2012	Signature: …….....
Jan Mueller-Berghaus (DE)	19 April 2012	Signature: …….....
Dalibor Valik (CZ)	19 April 2012	Signature: …….....
Barbara van Zwieten-Boot (NL)	19 April 2012	Signature: …….
Harald Enzmann (DE)	19 April 2012	Signature: …….....
Hubert Leufkens (NL)	19 April 2012	Signature: …….....

Article 6(12) referral of Commission Regulation (EC) no 1084/2003, as amended

Procedure No: EMEA/H/A-6(12)/1313

Ethinylestradiol-Drospirenone 24+4 and associated names (INN: ethinylestradiol/drospirenone)

Divergent statement

Based on the presented clinical evidence in their totality, I am of the following opinion:

A clinical relevant effect on moderate acne versus placebo was shown; the placebo-controlled trials were designed according to the regulatory recommendations for placebo-controlled trials; the absence of active controlled studies is considered acceptable as no alternative treatment option within the class of COCs can be identified and no suitable comparator was available for clinical trials.

Even if the relative risk of VTE for drospirenone-containing OCs is higher than for levonorgestrel-containing OCs the absolute risk of VTE is still very low. This risk level is acceptable for women seeking OCs. This risk in healthy non-COC users of fertile age is about 10 cases per 100.000 women years, OCs in healthy women increase this risk to 20-40 cases per 100.000 treatment years of COC-use (RR= 2-4). In women with additional risk factors the absolute numbers are higher, but that applies to all COCs.

The target population for moderate acne indication was limited to a group that is prescribed an oral contraceptive. However, to address the concern that there might be off-label use the MAH was prepared to initiate a risk minimisation program with an educational program and two utilisation studies. If the prescribing rate for treatment of moderate acne in women who are not seeking contraception is found greater than 10% in either drug utilisation study, the MAH would work with local health authorities and professional prescribing organisations to expand the educational efforts.

Other treatments in moderate acne have their limitations, topical/oral retinoids are contra-indicated in women of childbearing age because of teratogenic risks and prolonged antibiotic therapy carries a risk of inducing resistance and could reduce efficacy of hormonal contraception.

CHMP member expressing a divergent opinion:

Karsten Bruins Slot (NO)	**19 April 2012**	**Signature: ……..**