26 January 2017
EMA/174401/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Dienogest/ethinylestradiol containing medicinal products indicated in acne

INN: dienogest/ethinylestradiol

Procedure no: EMEA/H/A-31/1435

Note:

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

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1. Information on the procedure

On 18 February 2016 the UK Medicines and Healthcare products Regulatory Agency (MHRA) triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the benefit-risk balance of dienogest/ethinylestradiol (DNG/EE) in the acne indication given the existing concerns regarding the risk of venous thromboembolic events (VTE) with this combination and also taking into consideration the lack of adequate evidence on the efficacy. The CHMP was therefore requested to give its opinion on whether the marketing authorisations for dienogest/ethinylestradiol containing medicinal products 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".

2. Scientific discussion

2.1. Introduction

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.

The European reference product, Valette, was first granted a marketing authorisation in 1995. Valette and related generics contain 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".

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 European level, the 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.

The CHMP reviewed all data from clinical studies, published literature, clinical guidelines, post-marketing experience, including responses submitted by the marketing authorisation holders, on the efficacy and safety of dienogest/ethinylestradiol in the acne indication. Whilst all available data have been assessed, it should be noted that this report summarises only the most relevant data.

2.2. Data on clinical efficacy

Acne is one of the most common skin disorders. Acne affects more than 50% of teenagers and approximately 10% of the cases persist beyond the age of 25 years. The social, psychological, and emotional impairment that can result from acne may be severe. Scarring can lead to lifelong problems in regard to self-esteem.

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 4 pathophysiologic mechanisms are involved in the aetiology of acne:

1) Androgen-mediated stimulation of sebaceous gland activity;

2) Abnormal keratinisation leading to follicular plugging (comedo forming);

3) Proliferation of the bacterium *Propionibacterium acnes* (*P. acnes*) within the follicle;

4) Inflammation.

Despite numerous systems for the classification of acne severity, there is no universal standard (Tan 2008).

A 2008 publication (Hayashi, Akamatsu et al. 2008) classified acne based on the number of inflammatory lesions on half of the face as 0-5, “mild”; 6-20, ”moderate”; 21-50, “severe”; and more than 50, “very severe”.

The Combined Acne Severity Classification (Lehmann HP 2002) employs lesion counting and comprises three categories:

- Mild acne: fewer than 20 comedones, or fewer than 15 inflammatory lesions or a total lesion count lower than 30;
- Moderate acne: 20-100 comedones, or 15-50 inflammatory lesions or a total lesion count of 30-125;
- Severe acne: more than 5 cysts, or comedone count greater than 100, or a total inflammatory count greater than 50, or a total lesion count greater than 125.

Although acne is one of the most common skin disorders, its pathophysiology is poorly understood, and no consensus exists 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 dienogest/ethinylestradiol in the treatment of acne papulopustulosa is based on the data of 2 pivotal clinical phase III studies: A07062 (Valette versus Pramino (triphasic EE/norgestimate)) and A28501 (Valette versus Diane 35 versus placebo) (table 1). The primary efficacy parameters and the study duration of both studies were identical and the inclusion and exclusion criteria were quite similar.

Table 1 Overview of clinical phase III studies of DNG/EE in the treatment of acne papulopustulosa

Study id and design / reference	**Key objectives / endpoints** (cycle 6 compared to baseline)	**Population**	**Inclusion/ exclusion criteria**	**Treatment**	**Main efficacy results** EE/DNG vs. EE/NGM (1.FAS= full analysis set; 2. per protocol set)
Therapeutic indication: Acne papulopustulosa in female patients ***Phase III study (Valette vs. Pramino)***					
<u>*Study ID*</u> A07062 (Study Report Number) <u>*Design*</u> Phase III, multicenter,DB, random, parallel groups; testing for non-inferiority 50 centers (GE, AT, FR, PT, CZ, PL, BE, NL, HU, RO, BG)	**Primary Endpoints** -Change in inflammatory lesion count (%) -Change in total lesion count (%) -Proportion of patients with improvement of facial acne (investigator's global assessment) **Secondary Endpoints** -Sebumetry -Patient's global assessment -Investigator's global assessment for chest and back -Hormones -Safety	Mild to moderate acne papulopustulosa; females 16-40 y.; (total, n= 1041) EE/DNG (n=527) EE/NGM (n=514)	**Inclusion Crit.** -6 to 100 comedones, 10 to 50 papules and/or pustules and not more than 5 nodules in the face -Agreed to contraception and no contraindications against OC. -Washout of topical and systemic acne therapies -Avoidance of comedogenic make-up, sun-screen and anti-acne therapy **Exclusion C.** -Smokers > 30 y. -Pregnancy, lactation -Liver disease -Vascular and metabolic diseases -Malignant tumors	**Valette** (tablets), Ethinylestradiol 0.03 mg/ Dienogest 2mg (EE/DNG) vs. **Pramino** (tablets), Ethinylestradiol/ norgestimate (EE/NGM) both over 6 cycles (≈ 6 months); <u>Valette</u> 1 tablet/ d on day 1-21, no treatment on day 22-28. <u>Pramino</u> 1tablet/d on day 1-21, day 1-7: 0.035/0.180 mg EE/NGM day 8-14: 0.035/0.215 mg EE/NGM day 15-21: 0.035/0.250 mg EE/NGM	**Change in inflammatory lesion count**: -66.3% vs. -64.4% (p<0.001) -66.0% vs. -65.4% (p<0.001) **Change in total lesion count**: -58.3% vs. -57.2% (p<0.001) -57.7% vs. -54.9% (p<0.001) **Proportion** of patients with **improvement of facial acne**: 95.6% vs. 92.0% (p<0.001) 96.9% vs. 96.1% (p<0.001) NI-margin 10%

				No treatment on day 22-28	
Study id and design / reference	**Key objectives / endpoints (cycle 6 compared to baseline)**	**Population**	**Inclusion/ exclusion criteria**	**Treatment**	**Main efficacy results** EE/DNG vs. EE/CPA vs. placebo (1.FAS= full analysis set; 2. per protocol set)
Therapeutic indication: Acne papulopustulosa in female patients ***Phase III study (Valette vs. Diane 35 vs. placebo); publication of Palombo-Kinne et al. 2009***					
Study ID A28501 *Design* Phase III, multicenter, DB, random, parallel groups, 3 arms, double-dummy technique. Test vs. active control vs. placebo; Testing for NI resp. superiority against control resp. placebo 65 centers (Czech Republic, PL, Russian Federation, Slovakia, Ukraine)	**Primary Endpoints** -Change in inflammatory lesion count (%) -Change in total lesion count (%) -Proportion of patients with improvement of facial acne (investigator's global assessment) **Secondary Endpoints** -Sebumetry -Patient's global assessment -Investigator's static global at each visit -Safety	Mild to moderate acne papulopustulosa; females 16-45 y.; (total, n= 1338) EE/DNG (n= 530) EE/CPA (n=537) Placebo (n=267)	**Inclusion Crit.** -10 to 50 comedones, 10 to 50 papules and pustules together and not more than 3 small nodules -Agreed to contraception and no contraindications against OC. -Washout of topical and systemic acne therapies -Avoidance of comedogenic make-up, sun-screen and anti-acne therapy **Exclusion C.** -Smokers > 30 y. -Pregnancy, lactation -Body mass index >30 kg/m²	**Valette**, Ethinylestradiol/ Dienogest (EE/DNG) vs. **Diane 35**, Ethinylestradiol/ cyproteronacetate (EE/CPA vs. **placebo** over 6 cycles (≈ 6 months); 1 tablet/ d on day 1-21, no treatment on day 22-28.	**Change in inflammatory lesion count**: -65.6% vs. -64.6% vs. -49.5% (p*<0.05) -66.6% vs. -65.2% vs. -50.8% (p*<0.05) **Change in total lesion count**: -54.7% vs. -53.6% vs. -39.4% (p*<0.05) -55.4% vs. -54.3% vs. -40.2% (p*<0.05) Proportion of patients with **improvement of facial acne**: 91.9% vs. 90.2% vs. 76.2% (p*<0.05)

					93.7% vs. 92.1% vs. 79.1% (p*<0.05) P* < 0.05 for both superiority of EE/DNG to placebo and non-inferiority of EE/DNG to EE/CPA NI-margin 10%

2.2.1.1. Phase III study (Valette versus Pramino)

This was a multinational, multicenter, randomised, double-blind, controlled trial, study No A07062, where 1041 healthy women between 16 and 40 years of age with mild to moderate facial acne and no contraindication to COC use, received either DNG/EE (2mg/30µg) or triphasic EE/norgestimate (EE/NGM) in a 1:1 ratio for 6 cycles.

Study A07062 was conducted to demonstrate non-inferiority of DNG/EE as an acne treatment to triphasic NGM/EE (Pramino). EE/NGM is considered to be an adequate comparator to demonstrate non-inferiority as it contains the same active ingredients in identical concentrations and regimen as triphasic EE/NGM, which has been proven in placebo controlled trials to be effective in the treatment of mild to moderate acne papulopustulosa. Triphasic EE/NGM (Triafemi) is authorised in France for oral contraception in women with mild to moderate acne.

The secondary objectives were sebumetry, the patient's global assessment of effect on seborrhea and acne, the investigator's global assessment of effect on seborrhea and acne on the chest and back, bleeding pattern, hormone and sex hormone-binding globulin (SHBG) levels, photo documentation, and general safety.

A clinically significant difference in the lesion counts, and therefore the non-inferiority margin, in study A07062 was set to 10%: if the upper limit of the 95% two-sided confidence interval of the difference in relative changes in the lesion count for DNG/EE and the triphasic NGM/EE was less than 10%, the null hypothesis of inferiority had to be rejected and the alternative hypothesis of non-inferiority accepted.

Study A07062 is not placebo-controlled, however, there is historical evidence for assay sensitivity from two double-blind, randomized, placebo-controlled studies with EE/NGM ((Lucky, Henderson et al. 1997); (Redmond, Olson et al. 1997)).
With regards to the study groups, they both showed similar demographic and baseline characteristics.

According to criteria used for determining the severity of acne (see 2.2. Data on clinical efficacy), the inclusion and the mean lesion count at baseline in the study, moderate acne is considered to dominate in this study: At baseline in the full analysis set (FAS) population the mean inflammatory lesion count was 48.9 versus 48.4, and the inflammatory lesion count was 29.8 versus 29.4 for patients in the Valette and Pramino groups respectively.

<u>Patient disposition</u>

Patient disposition during the study showed a completion rate of 87.3% for DNG/EE and 86.4% for EE/NGM. The reasons for discontinuation were similarly distributed over the treatment groups. Discontinuation due to adverse events slightly higher in the EE/NGM group compared to DNG/EE (6.2% of the patients versus 4.3%).

Primary efficacy parameters

The three primary efficacy parameters were (each baseline compared to cycle 6):

- percentage of change in inflammatory lesion count;
- percentage of change in total lesion count;
- percentage of patients with improvement of facial acne according to IGA (Investigator's Global Assessment). IGA was a six-point scale (1= clear, 2= excellent improvement, 3= good improvement, 4= moderate improvement, 5= no improvement, 6= deterioration).

Results

According to the results for all three primary efficacy variables, the non-inferiority of DNG/EE to NGM/EE in the therapy of facial acne was demonstrated with a non-inferiority margin of 10% for all three variables (with $p<0.001$). Of note, the confidence intervals in study A07062 had a maximum upper limit of 3.8% (in case of the inflammatory lesion count of the per protocol set (PPS)). Please note that in the tables below SH T 659 A is Valette (DNG/EE) and EE2/NGM is EE/NGM:

TT 39: Summary of the analyses of the primary target variable 'relative change in inflammatory lesion count in percent'

	SH T 659 A mean	EE2/NGM mean	difference of means (SH T 659 A – EE2/NGM)	two-sided 95% confidence interval for difference of means	one-sided p-value for non-inferiority
PPS	-66.0	-65.4	-0.6	(-5.0; 3.8)	<0.001
FAS	-66.3	-64.4	-1.9	(-5.9; 2.2)	<0.001

TT 34: Summary of the analyses of the primary target variable 'relative change in total lesion count in percent'

	SH T 659 A mean	EE2/NGM mean	difference of means (SH T 659 A – EE2/NGM)	two-sided 95% confidence interval for difference of means	one-sided p-value for non-inferiority
PPS	-58.3	-57.2	-1.1	(-4.9; 2.8)	<0.001
FAS	-57.7	-54.9	-2.8	(-6.8; 1.1)	<0.001

TT 44: Proportion of assessed patients who showed improvement of their facial acne according to the investigator's global assessment

	SH T 659 A proportion (%)	EE2/NGM proportion (%)	difference of proportions (SH T 659 A – EE2/NGM)	two-sided 95% confidence interval for difference of proportions	one-sided p-value for non-inferiority
PPS	96.9	96.1	0.8	(-1.7; 3.4)	<0.001
FAS	95.6	92.0	3.5	(0.5; 6.5)	<0.001

For all three primary efficacy parameters DNG/EE was found to be non-inferior to EE/NGM. This is reflected in the upper limit of the two-sided 95% confidence interval for difference of means, which was less than 10.

To summarize, for the full analysis set the following results were obtained:

For inflammatory lesions, the reduction rates were -66.3% for DNG/EE and -64.4% for EE/NGM.
For total lesions, the reduction rates were -58.3% for DNG/EE and -57.2% for EE/NGM.
The percentages of patients with improvement of facial acne were 95.6% for DNG/EE and 92.0% for EE/NGM.

For all three primary efficacy variables, the results for the FAS were similar to those reported for the PPS. Moreover the effects reached in regard to reduction of inflammatory acne lesions and improvement of facial acne by IGA in this study were quite similar to the effects observed in the *verum* groups (DNG/EE and EE/CPA) in the Palombo-Kinne trial (see below).

Secondary parameters

Regarding the patient's global assessment of effect on facial acne, 92.4% of the patients in the SH T 659 A group and 90.4% in the EE2/NGM group reported an improvement of their facial acne (FAS). These results were very similar to the investigator's global assessment. The results for sebumetry suggested a slight decrease in sebum production. For the hormone parameters determined, a decrease in serum androgens, FSH and LH, and a favourable increase of SHBG (by its binding potential of free androgens) were observed.

2.2.1.2. Phase III study (Valette versus Diane 35 versus placebo), see Palombo-Kinne et al. 2009

The Palombo-Kinne et al. study (Palombo-Kinne, Schellschmidt et al. 2009) (A28501) was a multinational, multicenter, randomised, three-arm, double-blind, placebo-controlled trial, where 1326 healthy women between 16 and 45 years of age with mild to moderate facial acne and no contraindication to COC use, received either DNG/EE (2mg/30µg), EE/CPA (35µg/2mg) or placebo in a 2:2:1 ratio for 6 cycles. The primary efficacy parameters and the study duration were identical to the trial with Valette versus Pramino and the inclusion and exclusion criteria were quite similar. The comparator is a combined oral contraceptive and established acne treatment and the placebo-arm provides assay-sensitivity. In this study superiority of Valette in comparison to placebo and non-inferiority of Valette in comparison to Diane 35 was demonstrated statistically significant.

The harmonized indication of EE/CPA across the EU is:

"Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age […] after topical therapy or systemic antibiotic treatment has failed..[..].".

The harmonised EU indication of EE/CPA refers to acne only, not to oral contraception.

Demographics and baseline characteristics

The study groups showed similar demographic and baseline characteristics. All patients were Caucasian, except for one patient who was Asian. At baseline, the total numbers of acne lesions (mean± SD) were similar across groups (DNG/EE, 53.8±16.8; EE/CPA, 53.5±16.6; placebo 51.7±16.0). The same was true for the inflammatory lesions (DNG/EE, 22.9±10.5; EE/CPA, 22.7±10.1; placebo 22.0±10.0). The mean age was between 24 and 25 years in the treatment groups. Between 14% and 16% smokers were included in the treatment groups.

Patient disposition

The completion rates were 94.7% for DNG/EE, 95.3% for EE/CPA and 92.0% for placebo. The reasons for discontinuation were similarly distributed over the treatment groups, although the highest discontinuation rate was in the placebo group (8%, versus 5.3% for DNG/EE and 4.7% for EE/CPA). Discontinuation due to adverse events was infrequent in all groups (between 0.6% and 1.5%).

Primary efficacy parameters

Three primary efficacy parameters were evaluated:

- percentage of change in inflammatory lesion count;
- percentage of change in total lesion count;
- percentage of patients with improvement of facial acne according to IGA (Investigator's Global Assessment). IGA was a six-point scale (1= clear, 2= excellent improvement, 3= good improvement, 4= moderate improvement, 5= no improvement, 6= deterioration).

Results

All primary analyses proved superiority of DNG/EE to placebo and non-inferiority to EE/CPA ($p<0,05$). For the full analysis set the following results were obtained:

For inflammatory lesions, the reduction (± SD) rates were -65.6 ± 29.9% for EE/DNG, -64.6 ± 31.2% for EE/CPA and -49.4 ± 41.0% for placebo. For total lesions, the reduction rates were -54.7 ± 26.3% for DNG/EE, -53.6 ± 27.5% for EE/CPA and -39.4 ± 33.6% for placebo. The percentages of patients with improvement of facial acne were 91.9% for DNG/EE, 90.2% for EE/CPA and 76.2% for placebo.

In conclusion, in spite of the prominent placebo effects, DNG/EE was superior to placebo and as effective as EE/CPA in the treatment of mild to moderate acne. Similar effects were seen in the full analysis set and the per protocol set. A placebo-effect in trials with COC in female acne is known from other studies ((Redmond, Olson et al. 1997) and (Lucky, Henderson et al. 1997)).

2.2.2. Supportive Data

2.2.2.1. Cochrane review 2012 "Combined oral contraceptive pills for treatment of acne"

"Combined oral contraceptive pills for treatment of acne" (Arowojolu, Gallo et al. 2012), Cochrane Database of Systematic Reviews 2012; Issue 7, Art. No: CD004425.

This Cochrane review refers predominantly to published data; 31 trials with COCs in the treatment of acne are included with over 12.500 participants. One of the included trials refers to DNG/EE: The Palombo-Kinne trial (Valette versus Diane 35 versus placebo). Also the studies Lucky et al. and Redmond et al. were included into the Cochrane review. These two are important studies in regard to assay-sensitivity for the trial Valette versus Pramino (EE/NGM) of the marketing authorisation holder. The six COCs evaluated in placebo-controlled trials were: dienogest/EE (Valette), EE/levonorgestrel, EE/norethindrone acetate, EE/norgestimate, EE/drospirenone, EE/chlormadinone acetate).

The main results and conclusions were as follows:

Main results

The review includes 31 trials with 12,579 participants. Of 24 comparisons made, 6 compared a COC to placebo, 17 different COCs, and 1 compared a COC to an antibiotic. Of nine placebo-controlled trials with data for analysis, all showed COCs reduced acne lesion counts, severity grades and self-assessed acne compared to placebo. A levonorgestrel-COC group had fewer total lesion counts (MD -9.98; 95% CI -16.51 to -3.45), inflammatory and non-inflammatory lesion counts, and were more likely to have a

clinician assessment of clear or almost clear lesions and participant self-assessment of improved acne lesions. A norethindrone acetate COC had better results for clinician global assessment of no acne to mild acne (OR 1.86; 95% CI 1.32 to 2.62). In two combined trials, a norgestimate COC showed reduced total lesion counts (MD-9.32; 95% CI -14.19 to -4.45), reduced inflammatory lesion and comedones counts, and more with clinician assessment of improved acne. For two combined trials of a drospirenone COC, the investigators' assessment of clear or almost clear skin favored the drospirenone group (OR 3.02; 95% CI 1.99 to 4.59). In one trial, the drospirenone-COC group showed greater (more positive) percent changes for total lesion count (MD 29.08; 95% CI 3.13 to 55.03), inflammatory and non-inflammatory lesion counts, and papule and closed comedone counts. A **dienogest-COC** group had greater percentage decreases in total lesion count (MD -15.30; 95% CI -19.98 to -10.62) and inflammatory lesion count, and more women assessed with overall improvement of facial acne. A chlormadinone -COC group had more 'responders', those with 50% or greater decrease in facial papules and pustules (OR 2.31; 95% CI 1.50 to 3.55).

Differences in the comparative effectiveness of COCs containing varying progestin types and dosages were less clear, and data were limited for any particular comparison. COCs that contained chlormadinone acetate or cyproterone acetate improved acne better than levonorgestrel. A COC with cyproterone acetate showed better acne outcomes than one with desogestrel, but the studies produced conflicting results. Likewise, levonorgestrel showed a slight improvement over desogestrel in acne outcomes, but results were not consistent. A drospirenone COC appeared to be more effective than norgestimate or nomegestrol acetate plus 17β-estradiol but less effective than cyproterone acetate.

Authors' conclusions

This update yielded six new trials but no new change in conclusions. The six COCs evaluated in placebo-controlled trials are effective in reducing inflammatory and non-inflammatory facial acne lesions. Few important and consistent differences were found between COC types in their effectiveness for treating acne. How COCs compare to alternative acne treatments is unknown since only one 'underpowered trial addressed this issue' (Monk, 1987) (see Cochrane Review, p.9). "The use of standardized methods for assessing acne severity would help in synthesizing results across trials as well as aid in interpretation."

In regard to the **comparative effectiveness of COCs** the authors stated the following:

Differences were less clear in the comparative effectiveness of COCs containing varying progestin types and dosages. Although COCs containing CPA have been traditionally used for acne treatment (Seaman 2003), little evidence shows its superiority over other progestins. The CPA/EE combination appeared to improve acne (i.e., inflammatory lesions and global assessments) better than LNG/EE in the two trials that made this comparison (Lachnit-Fixson 1977; Carlborg 1986), but the findings had wide confidence intervals, which indicate limited precision. Also, the three trials that compared CPA/EE to DSG/EE produced conflicting results (Dieben 1994; Charoenvisal 1996; Vartiainen 2001). The COCs with CPA/EE were not significantly different from LNG/EE or DSG/EE in discontinuation rates due to adverse events.

And the **final conclusion** of the Cochrane review 2012 was:

Since COCs reduce acne lesion count, severity grades and self-assessed acne in placebo-controlled trials, they should be considered for women with acne who also want an oral contraceptive. COCs containing CMA or CPA seem to improve acne better than LNG; however, this finding is based on limited evidence. A DRSP-COC may be more effective than NGM or NOMAC/E2 but the trials used different methods to assess acne severity assessments. Comparisons between other COCs were either conflicting or showed no significant difference in their ability to reduce acne [...].

In conclusion, considering all data, efficacy of EE/DNG in the treatment of acne with moderate severity has been demonstrated.

2.2.3. Demonstrated benefits

The overall efficacy assessment of DNG/EE as a treatment for acne in females observed during studies A07062 and A28501 demonstrates statistically significant responses to DNG/EE as compared to EE/NMG, and EE/CPA and placebo respectively.

In study A07062, according to the results for all three primary efficacy variables, the non-inferiority of DNG/EE in the therapy of facial acne was demonstrated with a non-inferiority margin of 10% for all three variables (with $p<0.001$) underlined by the upper limits of the two-sided 95% confidence intervals for difference of means that were less than 10, each.

The Palombo-Kinne publication (Palombo-Kinne, Schellschmidt et al. 2009) provides further evidence for efficacy and safety of Valette in the acne indication in females. In this study Valette was superior to placebo and non-inferior to EE/CPA in female patients with mild to moderate acne papulopustulosa.

The inclusion criteria of both these trials confirm that predominantly moderate acne vulgaris dominated in the studies. Moreover, according to current treatment guidelines, COCs are not indicated in mild acne, they are considered as treatment alternatives in females with moderate to severe acne. Therefore the current indication of the originator Valette, which refers to moderate acne in females, is supported. For further wording of the indication see section 3. Benefit-risk balance.

The Cochrane review 2012 "Combined oral contraceptive pills for treatment of acne" (Arowojolu, Gallo et al. 2012) also concludes that all COCs evaluated in placebo-controlled trials, including Valette (DNG/EE) in the Palombo-Kinne trial (Palombo-Kinne, Schellschmidt et al. 2009) were effective in reducing inflammatory and non-inflammatory facial acne lesions, and that since COCs reduce acne lesion count, severity grades and self-assessed acne in placebo-controlled trials, they should be considered for women with acne who also want an oral contraceptive.

2.2.4. Uncertainty about benefits

There is a lack of clarity regarding the efficacy of DNG/EE when compared to other types of acne treatments i.e. topical and systemic antibiotics. A Cochrane review from 2012 (Arowojolu, Gallo et al. 2012) considered that there was a lack of clarity and no conclusions could be made regarding the effect of combined oral contraceptives when compared to an antibiotic. Findings from a recent meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris suggest that although antibiotics may be superior at 3 months, COCs (including DNG-containing) are equivalent to antibiotics at 6 months in reducing acne lesions and, thus, may be a better first-line alternative to systemic antibiotics for long-term acne management in women (Koo, Petersen et al. 2014). Nevertheless this meta-analysis includes only one small trial which directly compares an oral antibiotic to EE/CPA (Greenwood, Brummitt et al. 1985). This study was excluded from the Cochrane Review 2012 of COCs (Arowojolu, Gallo et al. 2012) in the treatment of acne due to "insufficient acne data reported".

Long-term efficacy data beyond 6 months of treatment are not available.

There are no completely consistent treatment guidelines for acne. For moderate acne papulopustulosa, according to the "European Evidence-based Guideline for the Treatment of Acne – Update 2016" (Nast, Dreno et al. 2016), topical therapies are 1st choice treatment and in case of a more widespread disease/ moderate severity an initiation of a systemic antibiotic treatment can be recommended

(medium strength of recommendation). Importantly, the European guideline does not recommend hormonal antiandrogens for moderate acne papulopustulosa. The European guideline considers hormonal antiandrogens plus topical treatment or plus topical treatment and an oral antibiotic as an alternative treatment in females with severe papulopustular/moderate nodular acne and severe nodular/conglobate acne (low strength of recommendation; oral isotretinoin being each 1st choice).

Whereas, the "Global Alliance to Improve Outcomes in Acne" (Gollnick, Cunliffe et al. 2003) sees oral antibiotics plus local therapies as 1st choice in all forms of moderate acne. According to this publication oral antiandrogens plus topical treatment are an appropriate alternative in females with all forms of moderate and severe acne. Both guidelines state, that the duration of treatment with systemic antibiotics should be limited to 3-4 months due to the potential risk of the development of antibiotic resistance.

2.3. Data on safety

2.3.1. Phase III trial: Valette (DNG/EE) versus Pramino (EE/NGM)

Safety

Safety variables in this study were physical, dermatological, and gynaecological examination (including cervical smear), medical and medication history, concomitant medication, pregnancy test, and adverse events (AEs).

Adverse events

A total of 1160 AEs were reported in 49.3% of the patients at the end of the study. The distribution of patients with AEs was similar between the two treatment groups (48.6% - DNG/EE group; 50% - EE/NGM group). Overall, the three most frequently reported AEs were nausea (in 8.9% of the patients), upper respiratory infections (8.0%), and headache (7.9%).

Treatment-related AEs

In a total of 25.2% of the patients, AEs were assessed as being related (possibly, probably, or definitely) to the study treatment (24.9% - DNG/EE group; 25.5% - EE/NGM group). The three most frequent treatment-related AEs (in both treatment groups) were nausea (in 6.8% of the patients), headache (4.6%), and breast enlargement (4.1%). The maximum intensity of AEs was assessed as moderate in 25.0%, mild in 17.7%, and severe in 5.8% of the patients. Most of the patients (38.9%) fully recovered from their AEs, 7.3% had not yet recovered, and 1.5% recovered with residual effects by the end of the study. Fifty-five AEs (5.3%) led to premature discontinuation of the study treatment.

Serious adverse events (SAEs)

No death occurred in the course of the study and the frequency of patients with SAEs in the two treatment groups was low. A total of eleven SAEs were reported in ten patients (1.0%).

The majority of SAEs in each treatment group were assessed as being not related to the study treatment by the investigators. One SAE in the DNG/EE group (degenerated uterine fibroids) and two SAEs in the EE/NGM group (psychic depression, schizophrenic reaction) were assessed as being possibly related to the study treatments (see below). With three exceptions, all patients had fully recovered from their SAEs by the end of the study. A total of four patients, i.e., two patients of the EE/DNG group and two patients in the EE/NGM group discontinued the study due to SAEs.

- DNG/EE group: Four SAEs occurred in four patients (0.8%) of the EE/DNG group
    - Degenerated uterine fibroids, possibly related to the study treatment

- EE2/NGM group: Seven SAEs occurred in six patients (1.2%) of the EE2/NGM group.
    - Psychic depression, possibly related
    - Schizophrenic reaction, possibly related

TT 74: Patients with SAEs by treatment

RNR	Country	HARTS term	Onset (weeks after treatment	Treatment relationship (investigator's	Discontinuation due to SAE
SH T 659 A					
[confidential info deleted]		Uterine fibroids degenerated	Week 3	Possible	Yes
[confidential info deleted]		Infection	Week 8	None	No
[confidential info deleted]		Infection	Week 6	None	Yes
[confidential info deleted]		Pneumonia	Week 6	None	No
EE2 / NGM					
[confidential info deleted]		Psychotic depression	Week 5	Possible	Yes
[confidential info deleted]		Gastroenteritis	Week 5	None	No (interrupted for 6 days)
[confidential info deleted]		Schizophrenic reaction	Week 4	Possible	Yes
[confidential info deleted]		Diarrhea	Week 18	None	No
[confidential info deleted]		Cyst	Approx. Week 12	None	No
[confidential info deleted]		Pyelonephritis	Week 9	None	No
[confidential info deleted]		Surgery	Week 18	None	No

NB: In the SAE-table above SH T 659 A is Valette (EE/DNG) and EE2/NGM is EE/NGM

Discontinuation due to AE

A total of 55 AEs (in 5.3% of the patients) led to discontinuation of the study treatment and, subsequently, premature discontinuation of the study. These were 23 AEs (in 4.4% of the patients) in the DNG/EE group and 32 AEs (in 4.4% of the patients) in the EE/NGM group. The most common reasons for discontinuation due to AE were acne, intermenstrual bleeding, and nausea.

TT 72: Most common reasons for discontinuation of study treatment due to AEs

HARTS term	SH T 659 A group (n= 527)		EE2/NGM group (n= 514)		Overall (n= 1041)	
	Patients with AE	[%] of patients	Patients with AE	[%]of patients	Patients with AE	[%]of patients
Acne	3	0.6	5	1.0	8	0.8
Headache	2	0.4	4	0.8	6	0.6
Intermenstrual bleeding	1	0.2	5	1.0	6	0.6
Nausea	2	0.4	3	0.6	5	0.5

Clinically significant changes in vital signs, weight, physical or gynaecological examination findings were rare and not related to either treatment.

Overall, a decrease in vaginal bleeding intensity (withdrawal and intra-cyclic bleeding) was observed in the treatment groups. The characteristics of vaginal bleeding for the DNG/EE group were slightly more favourable, but in general similar to those observed in the EE/NGM group.

2.3.2. Post marketing safety data

Palombo-Kinne trial, (Palombo-Kinne, Schellschmidt et al. 2009): Valette (DNG/EE) versus Diane 35 (EE/CPA) versus placebo

Safety variables in this study were amongst others adverse events, physical and gynecological examination body weight, vital signs and bleeding patterns.

Adverse events

AEs were reported in 32.4% of the patients in the DNG/EE group, 35.0% in the EE/CPA group and 32.6% in the placebo group (see table 3). The most frequent AEs among all groups were headache and nausea. The most frequent AEs seen in the COC groups were metrorrhagia, breast pain and breast tenderness. Nausea was relatively more frequent in the EE/CPA group. The intensity of the AEs was mostly mild to moderate.

Table 3
Most frequent adverse events (related and unrelated; number and percentage of affected patients)

	EE/DNG (*n*=525)	EE/CPA (*n*=537)	Placebo (*n*=264)
Total adverse events	170 (32.4%)	188 (35.0%)	86 (32.6%)
Most common adverse events			
Headache	28 (5.3%)	28 (5.2%)	14 (5.3%)
Nausea	22 (4.2%)	34 (6.3%)	7 (2.7%)
Vomiting	16 (3.0%)	21 (3.9%)	5 (1.9%)
Breast pain	11 (2.1%)	9 (1.7%)	–
Influenza	11 (2.1%)	14 (2.6%)	3 (1.1%)
Metrorrhagia	11 (2.1%)	<1.0%	–
Nasopharyngitis	9 (1.7%)	14 (2.6%)	8 (3.0%)
Breast tenderness	8 (1.5%)	15 (2.8%)	<1.0%
Respiratory tract infection	8 (1.5%)	<1.0%	–
Diarrhea	7 (1.3%)	11 (2.0%)	6 (2.3%)
Breast edema	<1.0%	11 (2.0%)	<1.0%
Weight increase	<1.0%	7 (1.3%)	<1.0%

The 10 most common adverse events are in the order of their frequency in the EE/DNG group. Events are given as MedDRA preferred terms.

Overall in the DNG/EE group, there were three (3) cases of serious adverse events compared to one (1) case in the CPA/EE group and two (2) cases in the placebo group. Out of the DNG/EE group, there was one case of ischemic stroke which was non-life threatening. This patient had a familial predisposition of cardiovascular events. There were no further serious adverse thromboembolic events.

Among the adverse events assessed as related to the study medication, there was only one serious adverse thromboembolic event reported from this study. It occurred in the DNG/EE group. The number of study patients included is relatively small (DNG/EE n=525 and EE/CPA n=537, placebo n=264) compared to the supposed frequency of thromboembolic events. Concerning the characterisation of the risk of thromboembolic events, no conclusions can be drawn for DNG/EE compared to other combined hormonal contraceptives.

2.3.3. Demonstrated risks

In the phase III trial Valette versus Pramino the total frequency of AEs was similarly distributed in the treatment groups. The five most frequent treatment-related AEs (in both treatment groups) were nausea (in 6.8% of the patients), headache (4.6%), and breast enlargement (4.1%), breast pain (3.6%), abdominal pain (2.8%) and weight gain (1.3%). The frequency of treatment related AEs was similar in both groups, only nausea was slightly more frequent in the EE/NGM group. The treatments used in this study were safe and well tolerated by the patients. The rate of patients who discontinued due to AEs was low. The most common reasons for discontinuation due to AE were acne, intermenstrual bleeding, and nausea; these AEs which led to drop-out were similarly frequent in the treatment groups. The number of SAEs was low (0.8% and 1.2% of the patients in the DNG/EE and EE/NGM groups respectively). No death and no case of venous thromboembolic events (VTE) occurred. None of the other safety parameters, including physical and gynecological examinations, vital signs, or weight gave rise to any safety concerns.

2.3.4. Uncertainty about risks

Venous thromboembolic events and arterial thromboembolic events (ATE) are considered to be serious although they occur rarely. Therefore it is important that an appropriate estimate of this risk is 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 DNG/EE is comparable, higher or lower in relation to other the combined hormonal 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). In comparison, cyproterone acetate has a number of 11 to 17 extra cases of thromboembolism per year per 10.000 treated women (Vinogradova, Coupland et al. 2015).

DNG/EE containing contraceptives were considered as part of a referral procedure under Article 31 (EMEA/H/A-31/1356) on combined hormonal contraceptives (CHCs) and it was concluded that the available data were insufficient to characterise the risk of VTE with dienogest/ethinylestradiol. To date there is insufficient data to clearly determine the risk for thromboembolic events compared to other combined hormonal contraceptives containing other progestogens. The lowest risk for developing VTE was shown for levonorgestrel-containing combined hormonal contraceptives. The safety data provided by marketing authorisation holders in the context of the ongoing referral however does not raise any new safety concern.

For dienogest containing CHC there is an additional study which was requested by the European Medicines Agency and is still ongoing. The INAS-SCORE Study (International Active Surveillance Study – Safety of Contraceptives: Role of Estrogens, NCT01009684) is an international, prospective, controlled, non-interventional, active surveillance, new user cohort study which was started in 25.000 women in Europe and then extended to the USA after the launch of the new regimen. The aim of the study is to assess the risks of short-term and long-term use of estradiol valerate and dienogest and of established oral contraceptives in a study population that is representative for the actual users of the different preparations. The primary outcomes of interest are cardiovascular events, in particular the incidence of VTE and ATE and acute myocardial infarction. The final study results will be available in 2017.

An additional meta-analysis looking into the risk of VTE for DNG/EE is also awaited. This meta-analysis will include the results from the INAS-Score study once they are available, in addition to the following three already finalised studies:

- Long-term Active Surveillance Study for Oral contraceptives (LASS),
- International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC) (Dinger, Bardenheuer et al. 2009),
- Transatlantic Active Surveillance on Cardiovascular Safety of Nuvaring (TASC) (Dinger, Mohner et al. 2013)

A limitation of the four studies is the fact that none of them was primarily designed to compare VTE incidence rates of DNG/EE to LNG/EE. Information submitted to date concerning the three finalized studies and the INAS-SCORE study is not complete and lacks important details that would be needed for a thorough evaluation of the meta-analysis to be performed with all four studies. A final conclusion about the risk of thromboembolic events for DNG/EE compared to other combined hormonal contraceptives can therefore not be drawn yet.

3. Benefit-risk balance

Efficacy

Efficacy of Valette (DNG/EE) has been demonstrated in two double-blind, randomized, controlled phase III trials in a total of more than 2300 female patients with mild to moderate acne papulopustulosa ("acne papulopustulosa" according to the study titles). One study compared Valette to EE/NGM, the other compared Valette to EE/CPA and placebo. Both studies had a similar design. Valette was non-inferior to both EE/NGM and EE/CPA. In the three-arm-study with EE/CPA, Valette in addition was superior to placebo. Although the study “Valette versus EE/NGM” had no placebo-arm, assay-sensitivity is considered to be sufficiently demonstrated by the marketing authorisation holder. In this study non-inferiority using a non-inferiority margin of 10% has been shown for all three primary efficacy parameters, i.e. reduction of total lesion count, reduction of inflammatory lesion count and percentage of patients with acne improvement by Investigator’s Global Assessment. Considering the inclusion criteria, which comprised minimum inflammatory and non-inflammatory lesion count, and the mean baseline acne lesion counts moderate acne vulgaris is considered to dominate in the phase III studies. Moreover, treating mild acne with systemic therapies, including COCs, is not in line with treatment guidelines. Therefore, DNG/EE should not be used for treatment of mild acne.

Guideline recommendations with regard to the use of COCs for the treatment of moderate acne are inconsistent. Importantly, treatment of moderate acne papulopustulosa by hormonal antiandrogens is not covered by the "European Evidence-based Guideline for the Treatment of Acne – Update 2016" (Nast, Dreno et al. 2016). According to this guideline, topical therapies are 1st choice treatment in moderate acne papulopustulosa and in case of a more widespread disease/ moderate severity an initiation of a systemic antibiotic treatment is recommended (medium strength of recommendation). While the European guideline does not recommend hormonal antiandrogens for moderate acne papulopustulosa, it does so as an alternative in combination with topical treatment resp. topical treatment plus an oral antibiotic in females with all forms of severe acne (including papulopustulosa) and in moderate nodular acne (low strength of recommendation).

In contrast, the "Global Alliance to Improve Outcomes in Acne" (Gollnick, Cunliffe et al. 2003) sees oral antibiotics plus local therapies as 1st choice in moderate acne papulopustulosa and mixed acne with oral antiandrogens plus topical treatment being an appropriate alternative in females with all forms of moderate and severe acne.

All in all, these are arguments for restricting the use of DNG/EE to 'moderate acne'.

There is very limited data comparing efficacy of COCs directly versus topical treatments or versus oral antibiotics. In the 2012 Cochrane review one small study comparing EE/CPA to minocycline was included (Monk et al., 1987), but the Cochrane review identified several shortcomings of this study. The Cochrane review (Arowojolu, Gallo et al. 2012) "Combined oral contraceptive pills for treatment of acne" stated, that all COCs evaluated in placebo-controlled trials, including Valette (DNG/EE) in the Palombo-Kinne trial (Palombo-Kinne, Schellschmidt et al. 2009) were effective in reducing inflammatory and non-inflammatory facial acne lesions. COCs containing CMA or CPA seemed to improve acne better than LNG; however, this finding was based on limited evidence. The final conclusion of the Cochrane review (Arowojolu, Gallo et al. 2012) was the following: "Since COCs reduce acne lesion count, severity grades and self-assessed acne in placebo-controlled trials, they should be considered for women with acne who also want an oral contraceptive.**"**

Findings from a recent meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris suggest that, although antibiotics may be superior at 3 months, COCs (including DNG-containing) are equivalent to antibiotics at 6 months in reducing acne lesions and, thus, may be a better first-line alternative to systemic antibiotics for long-term acne management in women (Koo, Petersen et al. 2014). Nevertheless this meta-analysis includes only one small trial which directly compares an oral antibiotic to EE/CPA (Greenwood, Brummitt et al. 1985). This study was excluded from the Cochrane Review (Arowojolu, Gallo et al. 2012) of COCs in the treatment of acne due to "insufficient acne data reported".

Taken together, the data and guideline recommendations support the use of DNG/EE as second line treatment in patients with moderate acne, when suitable topical therapies or oral antibiotic treatment have failed.

With regards to the duration of treatment, the CHMP agreed that treatment would be necessary for at least 3 months. This is considered justified in line with the results of the studies. An increasing effect has been seen with Valette cycle by cycle. In the publication referring to the trial with DNG/EE versus EE/CPA versus placebo (Palombo-Kinne, Schellschmidt et al. 2009) it is stated that relatively limited improvements occurred after cycle 1, larger improvements after cycle 3 and greater improvements after cycle 6. The most prominent effect on acne was seen after 6 months of treatment (both phase III trials). In view of the still to be quantified risk of VTE the CHMP agreed that women should be assessed 3-6 months after initiation of therapy and periodically thereafter to review the need for continuation of treatment. In addition to the information regarding duration of use, sections 4.3 and 4.4 of the SmPC already provide information on the increased risk for VTE, including risk factors, signs and symptoms including the risk associated with restarting after interruption or switching COCs.

At the start of the procedure the CHMP 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. Throughout the course of the assessment the CHMP agreed 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. The indication is in line with the study population of the phase III clinical trials and has been agreed by all marketing authorisation holders.

Safety

The adverse event profile of Valette and the comparator products in the phase III trials was very similar, and also frequencies were similar. The most common adverse events in both studies were headache and nausea, nausea being slightly more frequent in the EE/NGM and EE/CPA group compared to Valette. The rate of discontinuation due to AEs and the number of SAEs was low. No deaths and no cases of VTE occurred in the phase III studies. Nevertheless in the Palombo-Kinne trial

(Palombo-Kinne, Schellschmidt et al. 2009), there was one case of non-life-threatening ischemic stroke with a strong familial predisposition to cardiovascular events (considered related to DNG/EE; resolved at the end of the study). None of the other safety parameters, including physical and gynecological examinations, vital signs, or weight gave rise to safety concerns.

Concerning clinical safety, particularly the known risk to develop thromboembolic events, data provided for the period since finalisation of the Article 31 referral on combined hormonal contraceptives (EMEA/H/A-31/1356) in January 2014 to date are limited. Since then, no new safety concerns have become evident.

Additional risk minimisation measures had to be implemented by all marketing authorisation holders of combined hormonal contraceptives as a result of the aforementioned referral. Educational material had to be implemented including patient card, information for patients and checklist for prescription for physicians/healthcare professionals. The educational material contains a detailed description of the risk of thromboembolic events (VTE and ATE), general and individual risk factors, as well as the symptoms of thromboembolic events of which every woman using combined hormonal contraceptives should be aware of.

Furthermore, the educational material contains a recommendation to prescribe the combined hormonal contraceptive with the lowest risk of thromboembolic events, e.g. levonorgestrel containing products.

For dienogest-containing COCs, the relative risk to develop VTE or ATE compared to other progestogens is currently not clear as data from clinical / pharmacoepidemiological studies are limited.

There is still one study with dienogest ongoing, the INAS-SCORE study (NCT01009684), for which the final results are awaited in 2017. For further details to the studies already analysed for the different progestagens during the Article 31 referral on combined hormonal contraceptives please refer to the assessment report for referral number EMEA/H/A-31/1356.

Currently, the marketing authorisation holders involved in the DNG/EE referral do not propose any further additional risk minimisation measures; this is agreed by CHMP.

Benefit-risk balance

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 relevant 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 of DNG/EE 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 that the safety data provided by marketing authorisation holders 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 in the clinical trials after 6 months of treatment, paired with the still to be quantified risk of VTE, women should be assessed 3-6 months after treatment initiation and periodically thereafter to review the need for continuation of treatment.

4. Risk management

4.1. Risk minimisation activities

4.1.1. Amendments to the product information

The CHMP considered that amendments to sections 4.1 and 4.2 of the SmPC were necessary to include the information of this review.

The indication was restricted to the treatment of moderate acne after failure of suitable topical therapies or oral antibiotic treatment in women who elect to use an oral contraceptive.

In addition, the CHMP considered that a recommendation on the need for periodic assessment by the physician to assess the need for treatment continuation was needed.

The Package Leaflet was amended accordingly.

5. Grounds for 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 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 marketing authorisation holders 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.

In view of the above, the Committee considers that the benefit-risk balance of dienogest/ethynilestradiol-contanining medicinal products indicated in acne remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for dienogest/ethynilestradiol-contanining medicinal products indicated in acne.

REFERENCES

Arowojolu, A. O., M. F. Gallo, L. M. Lopez and D. A. Grimes (2012). "Combined oral contraceptive pills for treatment of acne." Cochrane Database Syst Rev(7): CD004425.

Dinger, J., S. Mohner and K. Heinemann (2013). "Cardiovascular risk associated with the use of an etonogestrel-containing vaginal ring." Obstet Gynecol **122**(4): 800-808.

Dinger, J. C., K. Bardenheuer and A. Assmann (2009). "International Active Surveillance Study of Women Taking Oral Contraceptives (INAS-OC Study)." BMC Med Res Methodol **9**: 77.

Gollnick, H., W. Cunliffe, D. Berson, B. Dreno, A. Finlay, J. J. Leyden, A. R. Shalita, D. Thiboutot and A. Global Alliance to Improve Outcomes in (2003). "Management of acne: a report from a Global Alliance to Improve Outcomes in Acne." J Am Acad Dermatol **49**(1 Suppl): S1-37.

Greenwood, R., L. Brummitt, B. Burke and W. J. Cunliffe (1985). "Acne: double blind clinical and laboratory trial of tetracycline, oestrogen-cyproterone acetate, and combined treatment." Br Med J (Clin Res Ed) **291**(6504): 1231-1235.

Hayashi, N., H. Akamatsu, M. Kawashima and G. Acne Study (2008). "Establishment of grading criteria for acne severity." J Dermatol **35**(5): 255-260.

Koo, E. B., T. D. Petersen and A. B. Kimball (2014). "Meta-analysis comparing efficacy of antibiotics versus oral contraceptives in acne vulgaris." J Am Acad Dermatol **71**(3): 450-459.

Lehmann HP, R. K., Andrews JS, Holloway V, Goodman SN. (2002). "Acne therapy: a methodologic review." J Am Acad Dermatol. **47**((2)): 231-240.

Lucky, A. W., T. A. Henderson, W. H. Olson, D. M. Robisch, M. Lebwohl and L. J. Swinyer (1997). "Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris." J Am Acad Dermatol **37**(5 Pt 1): 746-754.

Nast, A., B. Dreno, V. Bettoli, Z. Bukvic Mokos, K. Degitz, C. Dressler, A. Y. Finlay, M. Haedersdal, J. Lambert, A. Layton, H. B. Lomholt, J. L. Lopez-Estebaranz, F. Ochsendorf, C. Oprica, S. Rosumeck, T. Simonart, R. N. Werner and H. Gollnick (2016). "European evidence-based (S3) guideline for the treatment of acne - update 2016 - short version." J Eur Acad Dermatol Venereol **30**(8): 1261-1268.

Palombo-Kinne, E., I. Schellschmidt, U. Schumacher and T. Graser (2009). "Efficacy of a combined oral contraceptive containing 0.030 mg ethinylestradiol/2 mg dienogest for the treatment of papulopustular acne in comparison with placebo and 0.035 mg ethinylestradiol/2 mg cyproterone acetate." Contraception **79**(4): 282-289.

Redmond, G. P., W. H. Olson, J. S. Lippman, M. E. Kafrissen, T. M. Jones and J. L. Jorizzo (1997). "Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: a randomized, placebo-controlled trial." Obstet Gynecol **89**(4): 615-622.

Tan, J. K. (2008). "Current Measures for the Evaluation of Acne Severity." Expert Rev Dermatol. **3**((5)): 595-603.

Vinogradova, Y., C. Coupland and J. Hippisley-Cox (2015). "Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases." BMJ **350**: h2135.