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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ethinylestradiol/Drospirenon 24+4 0.02 mg/3 mg Berlipharm, film-coated tablets Berlipharm B.V., the Netherlands

ethinylestradiol/drospirenone

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1270/001/MR
Registration number in the Netherlands: RVG 100827

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Pharmacotherapeutic group:	hormonal contraceptives for systemic use; progestagens and estrogens, fixed combinations
ATC code:	G03AA12
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of first authorisation in NL:	11 October 2007
Concerned Member States:	Mutual recognition procedure with AT, BE, BG, CY, CZ, DE, DK, EE, EL, ES, FI, FR, IE, IS, IT, LT, LU, LV, MT, NO, PL, PT, RO, SE, SI, SK, UK MA withdrawal: BE (20-10-2011), CY (22-6-2012), EE (10-06-2011), EL (29-6-2012), IE (4-10-2011), LV (24-5-2011), LT (16-6-2011), LU (20-10-2011), NO (1-12-2013), RO (1-11-2011)
Application type/legal basis:	Directive 2001/83/EC, Article 8(3)

This report includes two annexes, on pages 24-37 and 38-49.

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SmPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ethinylestradiol/Drospirenon 24+4 0.02 mg/3 mg Berlipharm, film-coated tablets, from Berlipharm B.V. The date of authorisation was on 11 October 2007 in the Netherlands. The product is indicated for oral contraception.

A comprehensive description of the indications and posology is given in the SmPC.

Ethinylestradiol/Drospirenon 24+4 film-coated tablets contain ethinylestradiol (EE) in a dose of 20 µg and the progestagen drospirenone (DRSP) in a dose of 3 mg. DRSP is a synthetic steroid hormone with progestagenic and slight aldosterone-antagonistic and anti-androgenic activity. One Ethinylestradiol/Drospirenon 24+4 tablet is administered daily for 24 days followed by inert tablets for 4 days.

The combination of DRSP and EE is already approved for use in other oral contraceptives: Yasmin (NL license RVG 23827), containing 3 mg DRSP and 30 µg EE, and Yasminelle (NL license RVG 31781), containing 3 mg DRSP and 20 µg EE. The first marketing authorisation for Yasmin was granted in the Netherlands on 7 March 2000, and on 8 August 2000 in all EC countries involved at that time through a Mutual Recognition Procedure (MRP) with the Netherlands as Reference Member State (MRP NL/H/215/001).
Later, Yasminelle was developed to provide a formulation of Yasmin with a lower EE dosage of 20 µg. For Yasminelle an MRP was finalised in all EC countries on 2 May 2006 with the Netherlands as Reference Member State (MRP NL/H/701/001).
Ethinylestradiol/Drospirenon 24+4 has the same formulation as Yasminelle with the difference that Yasminelle is administered daily for 21 days, followed by a tablet-free interval of 7 days, while Ethinylestradiol/Drospirenon 24+4 is administered for 24 days, followed by the administration of an inert tablet for 4 days.

The contraceptive effect of Ethinylestradiol/Drospirenon 24+4 is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the endometrium.
In a therapeutic dosage, the synthetic progestagen drospirenone also possesses antiandrogenic and mild antimineralocorticoid properties. It has no estrogenic, glucocorticoid and antiglucocorticoid activity. There are indications from clinical studies that the mild antimineralocorticoid properties of Ethinylestradiol/Drospirenon 24+4 result in a mild antimineralocorticoid effect.

The marketing authorisation has been granted based on article 8(3) of Directive 2001/83/EC: a full application containing known active substances. Reference is made to the assessment of the identical registration dossiers of Yasmin and Yasminelle, where applicable.

The clinical documentation in support of this application consists of 4 phase III studies to support the indication of contraception and 2 phase III clinical studies, to support the sought indication *treatment of moderate to severe acne vulgaris in women seeking oral contraception*. This latter indication was not approved during the MRP or through the subsequent type II variation (see below).

Scientific advice was given by the MEB with respect to this product on 7 July 2005. This advice concerned the proposed indications.

Following closure of the MRP on 29 April 2008, the MAH submitted two variations:

- for addition of the indication *Treatment of emotional and physical symptoms of Premenstrual Dysphoric Disorder in women seeking oral contraception* (NL/H/1270/001/II/003).
- for addition of the indication *Treatment of moderate acne vulgaris only in women seeking oral contraception* (NL/H/1270/001/II/006).

The assessment and subsequent withdrawal of the first variation are discussed in Annex I to this PAR.
In Annex II the refusal of the acne indication is addressed.

No paediatric development programme has been submitted, as it was not yet required at the time of dossier submission.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substances
The active substances are drospirenone and ethinylestradiol, both established active substances of which ethinylestradiol is described in the European Pharmacopoeia (Ph.Eur.*). Drospirenone is a white to almost white powder, which is optically active and has 10 asymmetric centres. Ethinylestradiol is a white to off-white powder, present as ethinylestradiol-betadex-clathrate complex. Ethinylestradiol (EE) has five chiral centres.

Full data on the synthesis and quality control have been provided for drospirenone. The CEP procedure is used for ethinylestradiol. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacture
Drospirenone is prepared in a 16 step synthesis, including one microbiological, several chemical and four purification steps. Sufficient information on the synthesis, including critical steps has been provided. EE-betadex-clathrate is manufactured in a one step synthesis from EE.

Quality control of drug substances
The specifications of the drug substances are sufficient given the specific route of syntheses. Specifications for particle size have been included for both substances. Batch analytical data demonstrating compliance with this specification have been provided for 13 batches of drospirenone and for 9 batches of ethinylestradiol.

Stability of drug substance
Stability data of drospirenone and EE-betadex-clathrate has been obtained during storage at 25 ºC/60% RH, 30 ºC/70% RH and 40 ºC/75% RH. The substances were adequately stored. Both substances were stable with respect to degradation, temperature and light. Based on the data provided, a re-test period of 5 years could be granted, with no additional storage conditions, for both drug substances.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Ethinylestradiol/Drospirenon 24+4 0.02 mg/3 mg Berlipharm, film-coated tablets contain as active substance 0.02 mg ethinylestradiol (as betadex clathrate) and 3 mg drospirenone.
The active tablet is light pink, round with convex faces, one side embossed with the letters "DS" in a regular hexagon.

The 4 placebo (inactive) film-coated tablets contain no active substances. The placebo tablet is white, round with convex faces, one side embossed with the letters "DP" in a regular hexagon.

The film-coated tablets are packed in a transparent PVC/Aluminium blister in a cardboard wallet. Each blister contains 24 light pink active film-coated tablets and 4 white placebo film-coated tablets.

The excipients are:
Tablets containing EE/DRSP
Core: lactose monohydrate, maize starch, magnesium stearate (E470b)
Coating: hypromellose (E464), talc (E553b), titanium dioxide (E171), iron oxide red (E172)

Tablets not containing active substances (placebo tablets)
Core: lactose monohydrate, povidone K25, maize starch, magnesium stearate (E470b)
Coating: hypromellose (E464), talc (E553b), titanium dioxide (E171)

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Both drug substances are used in micronised form. Ethinylestradiol is used in the form of a clathrate with betadex for stability reasons. All excipients used are common in the manufacture of film-coated tablets. The packaging is usual and suitable for the product at issue.

Manufacturing process
Ethinylestradiol/Drospirenon 24+4 tablets are manufactured using a fluid bed granulation, tabletting and film-coating process. Adequate in-process controls are included and the process has been sufficiently validated. Placebo tablets are also manufactured using a fluid bed granulation, tabletting and film-coating process. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for 3 full-scale batches in accordance with the relevant European guidelines.

Excipients
All excipients comply with the Ph.Eur., except for ferric oxide which complies with the National Formulary (NF). These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification of EE and drospirenone, assay, content uniformity, dissolution, degradation products, and microbial quality. The product specification for the placebo tablets includes tests for appearance, identification of titanium dioxide, weight uniformity, disintegration, absence of EE and drospirenone, and microbiological quality. Satisfactory validation data for the analytical methods have been provided. Batch analysis data have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data have been obtained during storage at 25 ºC/60% RH, 30 ºC/65% RH and 40 ºC/75% RH. A slight decrease in EE assay and increase in degradation products is seen at long-term and intermediate storage conditions. Based on the provided stability data, the proposed shelf-life of 5 years could be granted. No additional storage conditions are necessary.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose and magnesium stearate, both with a theoretical risk of transmitting BSE, are considered risk free. Lactose is derived from milk for human consumption (EMA 410/01 rev 1) or calf rennet (EMA/CPMO/571/02) and magnesium stearate is of vegetable origin.

II.2 Non-clinical aspects

The non-clinical information is identical to that of Yasminelle (NL/H/701/01). This is agreed, since Ethinylestradiol/Drospirenon 24+4 and Yasminelle contain the same active compounds in a similar formulation and both products have the same route of administration.

Good Laboratory Practice
All pivotal toxicity studies and some toxicokinetic studies were compliant with standards of Good Laboratory Practice (GLP).

Pharmacology
The majority of the pharmacological studies were focused on drospirenone, as ethinylestradiol was considered to be a well-known drug. Some of the studies also tested the combination. Receptor binding studies and *in vitro* and *in vivo* biological assays for a range of hormonal effects in animals showed that drospirenone is a potent synthetic progestogen with antimineralocorticoid and anti-androgenic activity. Affinity for the progesterone receptor and *in vivo* antimineralocorticoid activity were not affected by ethinylestradiol. Drospirenone showed no androgenic, oestrogenic, gluco- and antiglucocorticoid activity.
Furthermore, drospirenone had no effect on smooth muscle *in vivo* or *in vitro* and had no relevant effects on central nervous function, pulmonary parameters, blood pressure, cardiovascular function, gastrointestinal motility or renal function. In rats, no effect of drospirenone was found on hormone-deficiency induced trabecular bone loss or on the bone protective effect of 17 β-oestradiol. Pharmacodynamic interactions with smooth muscle stimulating drugs and neurotropic drugs did not indicate clinically relevant interactions. Based on the relative antialdosterone activity of drospirenone as compared to spironolactone in animals, an additive effect on serum potassium can be expected if spironolactone and drospirenone are combined at pharmacologically active doses, but the dose of 3 mg drospirenone in Ethinylestradiol/Drospirenon 24+4 is below therapeutically active doses with respect to aldosterone antagonism. The major metabolites did not or only marginally bind to the steroid hormone receptors and are therefore not likely to have significant pharmacological effects *in vivo*.

Pharmacokinetics; metabolism
In an *in vitro* study with human liver microsomes and in genetically engineered lymphoblast cells expressing human liver CYP3A4, only little metabolism of drospirenone was found, suggesting that cytochrome P450 enzymes only play a minor, if any, role in the biotransformation of drospirenone.

Experiments in genetically engineered V79 cells and human lymphoblast cells expressing a number of human P450 enzymes suggested that drospirenone only inhibits these enzymes at concentrations above those found in humans after the recommended dose and therefore no significant *in vivo* inhibition of the biotransformation of ethinylestradiol by CYP3A4 is expected.

Toxicology
In animal experiments, drospirenone and ethinylestradiol elicited effects typical for the pharmacodynamic action of estrogens and/or progestagens.

The overall conclusion from reproductive studies is that as embryotoxic and fetotoxic effects in rats and monkeys were found at doses equivalent to the recommended human dose, the use of the combination of drospirenone and ethinylestradiol during pregnancy should be considered as potentially harmful to the unborn child. A warning is included in the SmPC.

A complete set of mutagenicity data on the active compounds and impurities revealed no evidence for genotoxic potential.

Carcinogenity studies regarding clinical safety show no unexpected carcinogenic properties of the combination.

Environmental risk assessment
The MAH has provided an expert report, based on the Environmental Risk Assessment (ERA) guideline (CPMP/SWP/4447/00-final). Ethinylestradiol/Drospirenon 24+4 tablets contains ethinylestradiol and drospirenone. For these sexual hormones the Phase I action limit does not apply. However, additional information is still needed regarding both ethinylestradiol and drospirenone for a Phase II tier A assessment according to the final guideline for environmental risk assessment of medicinal products (CHMP 2006). The MAH committed to complete these studies and to provide the Authorities with the risk assessment report. This commitment has been partially fulfilled (NL/H/1270/001/II/014).

II.3 Clinical aspects

Introduction
The combination of the drug substances DRSP and EE has previously been approved for use in Yasmin film-coated tablets (3 mg DRSP and 30 micrograms EE) and its low-dose formulation Yasminelle, in which the amount of EE is reduced from 30 micrograms to 20 micrograms.

The MAH's rationale of the development program of Yasminelle and Ethinylestradiol/Drospirenon 24+4 is to provide a formulation of Yasmin with a lower EE dosage of 20 micrograms. Experience with marketed combined oral contraceptives (COCs) demonstrate that, while maintaining the contraceptive reliability, the bleeding control properties are still acceptable for most users, if the daily EE dose is reduced from 30 micrograms to 20 micrograms.

The contraceptive effect of Ethinylestradiol/Drospirenon 24+4 is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the endometrium.

The clinical documentation in support of this application consists of 4 phase III studies to support the indication of contraception and 2 clinical phase III studies, to support the indication of treatment of moderate acne vulgaris. With regard to pharmacodynamic and pharmacokinetic documentation, cross-reference was made to the information in the registration dossiers of Yasmin and Yasminelle.

Quality of clinical studies, compliance with GCP
The MEB has been assured that GCP standards were followed in an appropriate manner in the studies conducted. The formulation of the batches used in key clinical studies are considered equivalent to that proposed for marketing.

Pharmacokinetics
No new studies have been performed. Reference is made to the registration files of Yasmin and Yasminelle. As there is no change in composition/dose, but only an increase in the number of active treatment days per cycle from 21 days in Yasminelle to 24 days per cycle in Ethinylestradiol/Drospirenon 24+4, the absence of new pharmacokinetic studies is acceptable.

Pharmacodynamics

Inhibition of ovulation
The MAH performed one new ovulation inhibition study in which the design and choice of variables are in accordance with the CHMP Note for Guidance on clinical investigation of steroid contraceptives in women. The results demonstrated that in comparison with Yasminelle, Ethinylestradiol/Drospirenon 24+4 results in a slightly higher degree of ovulatory inhibition, which can be explained by the longer active treatment per cycle of 3 more days (24 vs 21 days/per 28-day cycle). Additionally, as expected, after pre-defined dosing errors in both regimens in cycle 3 (i.e., 3 missed tablets on days 1 to 3) the decrease in ovulatory

inhibition was only very slight in the Ethinylestradiol/Drospirenon 24+4 group, whereas in the Yasminelle group a clinically relevant increase in ovulations was noted.

Hormone levels

The change from baseline to cycle 6 was measured for total testosterone, free testosterone, SHBG, and androstenedione in a subpopulation of subjects in one of the two acne studies (A25083) (18 subjects in the DRSP/EE group and 18 subjects in the placebo group). There was a statistically significant decrease in the mean change from baseline to endpoint in free testosterone in the DRSP/EE group compared with the placebo group (p=0.0024). There was a statistically significant increase in the mean change from baseline to endpoint in SHBG in the DRSP/EE group compared with the placebo group (p=0.0022). These hormonal changes were to be expected with low dose oral contraceptives. None of the other hormones evaluated showed any statistically significant differences between treatment groups.

Clinical efficacy

Indication 1: Contraceptive efficacy

The clinical dossier consisted of 4 phase III studies, of which the large long-term uncontrolled studies are considered pivotal.

Table E1: Overview of clinical phase III studies evaluating the efficacy of Ethinylestradiol/ Drospirenon 24+4 0.02 mg/3 mg Berlipharm (DRSP/EE) as an OC

Study	Short title / design	Treatment and total number of women by treatment group (full analysis set)	Treatment duration
A12007	*Pearl Index* *Multicenter, open, uncontrolled*	DRSP/EE: 1,027	13 cycles
A30713	*Pearl Index* *Multicenter, open, uncontrolled*	DRSP/EE: 1,101	13 cycles
A29551	Bleeding pattern and cycle control Multicenter, open, randomized, parallel comparison	DRSP/EE: 229 Mercilon®: 220	7 cycles
A09151	Lipid, hemostatic and carbohydrate profile Single-center, open-label, randomized, controlled	DRSP/EE: 29 Mercilon®: 30	7 cycles

Primary/secondary endpoints

Table E2 summarises the efficacy variables of the phase III studies relevant to the use of Ethinylestradiol/Drospirenon 24+4 as OC:

Table E2 : Overview of efficacy parameters to support the indication of Ethinylestradiol/ Drospirenon 24+4 0.02 mg/3 mg Berlipharm as an OC.

Pregnancies (studies A12007, A30713, A29551, A09151)
Pearl Index calculation (contraceptive reliability) A human chorionic gonadotropin (HCG) urine test had to be performed by all women before first tablet intake and if throughout the study no bleeding occurred until day 7 (studies A12007, A30713 and A29551) or day 4 (Mercilon®, study A09151) of the subsequent cycle. In case of a (suspected) pregnancy, immediate reporting to the sponsor was to follow and a pregnancy report form had to be filled in. In studies A30713 and A29551, an additional HCG urine test was performed at the study center at the final visit in order to detect pregnancies at the end of study. (Note: in study A12007, a pregnancy test had to be performed in every cycle in Austria; in the US, the pregnancy test was to be performed at the study site rather than at home. In study A29551, a pregnancy test had to be performed in every cycle in Austria.)
Bleeding pattern and cycle control parameters (studies A12007, A29551, A09151)
Bleeding pattern calculation of the number of - bleeding/spotting days - number of spotting only days - number (mean length, maximum length, range of length) of bleeding/spotting episodes - number (mean length, maximum length, range of length) of spotting only episodes Women daily recorded bleeding (including bleeding intensity*)* throughout the treatment phase using diary cards; the completed diary cards were collected.
Cycle control parameters calculation/completion of - withdrawal bleeding (yes/no, length, maximum intensity and onset of withdrawal bleeding episodes) - intracyclic bleeding (yes/no, number, maximum length and maximum intensity of intracyclic bleeding episodes, number of intracyclic bleeding days) - women with intracyclic bleeding Women daily recorded bleeding (including bleeding intensity) throughout the treatment phase using diary cards; the completed diary cards were collected.
Subjective assessment / quality of life (studies A12007, A30713, A29551, A09151)
At the final examination, either in case of premature discontinuation or after cycle 13 (studies A12007 and A30713) or cycle 7 (studies A29551 and A09151), the woman gave a subjective assessment of her well-being. She was to be asked to give a rating of her overall satisfaction with the study medication, of her physical and emotional well-being throughout the study compared to the time before the study, and if given a choice, whether she would continue with the study medication.
Treatment compliance (studies A12007, A30713, A29551, A09151)
The women were to record tablet intake daily on their diary cards. The completed diary cards were to be collected, reviewed, and signed by the investigator. Additionally, the women were to return all used, partly used, or unused blisters to the investigator. The diary entries were to be consistent with the balance of issued and returned medication (blisters) as recorded. A written explanation was to be submitted for any uneven balance between dispensation, use, and return.

Study participants

- General inclusion/exclusion criteria

Healthy women between 18 and 35 years, smokers maximum age of 30 at inclusion, Papanicolaou (Pap) smear taken or non-suspicious Pap smear within the last six months prior to start, and at least three cycles had to follow delivery, abortion, or lactation before start of treatment, were included.
Exclusion was mainly focussed on pregnancy, lactation, presence of liver disease, vascular disease, uncontrolled thyroid disorder, uncontrolled hypertension, diabetes mellitus, tumours (known or suspected), other severe diseases that might interfere, substantial overweight [study A12007: body mass index (BMI) > 35 kg/m^2, studies A30713, A29551 and A09151: BMI >30 kg/m^2], prohibited concomitant medication.

Patient instructions missed pill/vomiting or diarrhoea

During the treatment cycles, the volunteer is to take one tablet of the medication daily for 28 consecutive days. The next blister is to be started the day after the last tablet of the preceding blister without a break between cycles.
In the first treatment cycle, after having a negative HCG-home test, the first tablet was to be taken on the first day of withdrawal bleeding (= first day of the cycle), for both COC starters and switchers.

The tablet interval should not be exceeded by more than 12 hours, otherwise contraceptive protection might be compromised. In case of missed tablets, the volunteer had to take the missed tablet as soon as she remembered, at the latest with the next tablet. If she was less than 12 hours late in taking one of the hormone tablets, contraceptive protection was not reduced. If she was more than 12 hours late in taking any of the hormone tablets, contraceptive protection could be reduced.

Missed tablet management is based on the following basic rules:

1. Intake of hormone-containing tablets must never be discontinued for longer than 7 days.
2. Seven days of uninterrupted tablet taking are necessary to attain adequate suppression of the hypothalamic-pituitary-ovarian axis.

Therefore the following advice is given in daily practice:

Days	**General recommendations if the volunteer is 12 hours or more than 12 hours late in taking the pill:** Take the last missed tablet as soon as she remembers even if this means taking 2 tablets at the same time Continue tablet intake as usual
1-24	In addition: **back-up contraception** should be used **for the next 7 days**
25-28	**No back-up contraception** necessary

However, post approval the time window for missed pills has been extended from 12 hours to 24 hours through variation NL/H/1270/001/II/030, approved on 9 January 2013.

If the woman had missed tablets and subsequently had no withdrawal bleeding from day 24 by day 7 of the next cycle (inclusive), the possibility of a pregnancy should have been considered. Pregnancy was to be ruled out by a HCG test immediately. The woman had to perform a HCG-urine test at home or the investigator/a gynaecologist had to rule out pregnancy.
If the volunteer vomited within 4 hours after tablet intake, absorption might have not been complete. In such an event, another hormone tablet had to be taken from the reserve blister. The same procedure applied for diarrhoea.

Statistical methods

Calculation of the Pearl Indices (PI)

- **Overall Pearl Index (based on pregnancies due to method failure and pregnancies due to patient failure)**
  Contraceptive effectiveness was assessed by the PI for cycles in which no additional contraceptive method was used. The unadjusted PI and the corresponding 95% CI were calculated. Additionally, an adjusted PI (PI_c) was calculated taking intake failure into account.

  The PI was defined as the number of pregnancies divided by the exposure in woman years multiplied by 100 as follows:
  Number of pregnancies during treatment x 100/ exposure time (woman years) without backup contraception

  All women of the FAS, i.e. all women who had taken at least 1 dose of study medication and had at least 1 post-baseline observation, were included in the calculation of the PI. The length of the drug-

free interval, i.e. 4 days, was added for each woman. Hence, treatment exposure for Ethinylestradiol/Drospirenon 24+4 was defined as:

$$\text{treatment exposure} = (\text{day}_{\text{last}} - \text{day}_{\text{first}} + 1) + 4$$

where day_{last} was defined as the last day of pill intake and $\text{day}_{\text{first}}$ was the first day of pill intake. It should be noted that this time period was calculated regardless of treatment interruptions. The same rule applied to women who dropped out of the study prematurely. There were 2 exceptions to this rule:

- treatment exposure after conception was not counted
- treatment exposure during cycles in which additional contraceptive measures (backup contraception) were taken was not counted.

A pregnancy for which the day of conception was not later than 4 days after the last day of pill intake will be regarded as 'during treatment'. This is also the reason why 4 days were added to treatment exposure for each non-pregnant woman.

- **Calculation of the Pearl Index for method failure (PI_c)**

A treatment cycle was compliant if all 28 pills have been taken on 30 successive days, i.e. the cycle length did not exceed 30.

A pregnancy was considered as a method failure unless

- the estimated day of conception was in a non-compliant cycle or
- a method failure could be excluded on the basis of the comments on the pregnancy report form.

For the calculation of time of 'correct treatment exposure', cycles that were not considered compliant or where backup contraception was used were excluded. The PI_c and the corresponding upper confidence limit were calculated using the same methods as for the unadjusted PI.

Life table analysis (Kaplan Meier estimator)

In addition to the calculation of the PI, a life table analysis was performed for the time to the occurrence of a pregnancy. The cumulative failure rate, i.e. the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of pregnancies which were considered as 'during treatment'. The time (in days) from first day of pill intake until the last day of pill intake, the estimated day of conception, respectively, was used for the calculation of the Kaplan Meier product limit estimator.

- **Results on contraceptive reliability**

The number of pregnancies observed in the pivotal clinical trials are given in table E3. In the pivotal efficacy studies A12007 and A30713, 16 pregnancies were considered as during treatment (study A12007 with 11 pregnancies and A30713 with 5 pregnancies). In the other two studies, A29551 and A09151, no pregnancy was observed during Ethinylestradiol/Drospirenon 24+4 treatment. All pregnancies occurring during, before and after treatment with Ethinylestradiol/Drospirenon 24+4 were included in the calculation of the PI.

Table E3: Pearl Index (PI) and adjusted Pearl Index (PI_c) – pooled data of studies A12007, A30713, A29551 and A09151

	PI	PI_c
Total time of exposure (days / wy)	742,432 / 2,039.6	742,432 / 2,039.6
Backup contraception (days / wy)	12,895 / 35.4	
Non-compliant and/or backup contraceptive cycles (days / wy)		125,825 / 345.7
Relevant exposure time (days / wy)	729,537 / 2,004.2	616,607 / 1,694.0
Number of pregnancies	16	7
PI	**0.80**	
Upper two-sided 95% confidence limit of PI	**1.30**	
PI_c		**0.41**
Upper two-sided 95% confidence limit of PI_c		**0.85**

Overall Pearl Index

Based on the pooled analysis across all 4 phase III clinical studies, the overall Pearl Index (unadjusted PI) for Ethinylestradiol/Drospirenon 24+4 calculated on the basis of 16 pregnancies observed during treatment and a treatment exposure of 729,537 days (corresponding to 2,004.2 wy) is 0.80 with an upper one-sided 97.5% Confidence Interval (CI) of 1.30 which is equal to the upper limit of the corresponding two-sided 95% CI.

This result is in accordance with the CHMP 'Guideline on Clinical Investigation of Steroid Contraceptives in Women' (EMA/CPMP/EWP/519/98 Rev 1), which stipulates that the difference between the upper limit of the two-sided 95% CI and the corresponding point estimate of the PI should not exceed 1. This result was supported by the life table analysis.

Pearl Index for method failure

The PIc (PI for method failure) calculated on the basis of 7 pregnancies rated as method failure and a treatment exposure of 616,607 days (corresponding to 1,694.0 wy) in the Ethinylestradiol/Drospirenon 24+4 studies is 0.41 with an upper two-sided 95% confidence limit of 0.85.

The study size requirements and pregnancy reporting of the NfG on clinical investigation of steroid contraceptives in women regarding efficacy for a new contraceptive method are considered fulfilled:

- The calculation of efficacy was based on the Pearl Index and life table analysis.
- The difference between the point estimate and the upper limit of the 95% confidence interval does not exceed 1.
- At least 400 women have completed one year of treatment.
- No relevant differences were present in demography between the women in the Ethinylestradiol/Drospirenon 24+4 and Mercilon® groups, respectively.

Cycle control (bleeding pattern)

The comparative study performed for this purpose is considered of adequate design and the selection of bleeding variables to be collected by registration in daily diaries is acceptable. The choice of the comparator is acceptable, as Mercilon® is also a COC with lowered EE dose (20 µg ethinylestradiol + 150 µg desogestrel), although Yasminelle would also have been an adequate choice.

The results obtained on percentage of withdrawal- and intercyclic bleeding in the comparative study versus Mercilon® did not indicate any relevant differences between groups.

Indication 2: Treatment of moderate acne vulgaris in women seeking oral contraception

Proof of the clinical efficacy of Ethinylestradiol/Drospirenon 24+4 in the treatment of moderate acne vulgaris is based on the data of 2 pivotal clinical placebo-controlled phase III studies: A25083 and A25152 (table E4). The studies were identical with respect to their design and study course except for additional hormone measurements that were performed in a subgroup of approximately 40 women in study A25083, i.e. the change from baseline to cycle 6 in total testosterone, free testosterone, dehydroepiandrosterone sulphate, androstenedione and SHBG was also assessed for a subgroup of women.

A summary of design, number of participants, treatments and end points is presented in the table below:

Table E4: Overview of clinical phase III studies to demonstrate the efficacy of Ethinylestradiol/Drospirenon 24+4 0.02 mg/3 mg Berlipharm (DRSP/EE) in the treatment of moderate acne vulgaris

Study	Short title/design	Total number of women by treatment group*	Treatment duration	Efficacy parameters
A25083 **US**	moderate acne vulgaris multicenter, double-blind, randomized, placebo-controlled	DRSP/EE: 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 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	DRSP/EE: 222 Placebo: 215	6 cycles	

T* 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)

Inclusion- and exclusion criteria
In both studies A25083 and A25152, similar inclusion and exclusion criteria were utilized:

Inclusion criteria

- women in good general health, between 14 and 45 years old, ≥ 1 year post-menarche, requesting treatment for moderate acne vulgaris,
- no contraindications for OC use
- Smokers were to be recruited only up to a maximum age of 30 years.
- 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 ISGA scale[1].

[1] 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; 3 = lesions predominate, with multiple inflammatory lesions evident: Several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion; 4 = inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulocystic lesions; 5 = highly inflammatory lesions predominate: variable number of comedones, many papules/ pustules and nodulocystic lesions.

- 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 (e.g. Norplant®) or hormonal contraceptive intrauterine devices/systems (e.g. Mirena®)
  - two months free of oral contraceptives
  - six months free of systemic isotretinoin (e.g. Accutane®) or injectable contraception (e.g. Depo-Provera®)
  - 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)

Methodology
The methods of dermatological assessment, the study design and the efficacy variables were similar in both clinical studies. As no relevant differences could be observed between the individual study results and the pooled analysis, results of the pooled analysis are summarized and discussed below.

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

The endpoint for efficacy analysis was visit 5 (day 17 – 24 of cycle 6), with missing values replaced by the last observed value carried forward.

Table E5 summarizes the methods applied to evaluate the primary efficacy variables of studies A25083 and A25152 relevant to the use of Ethinylestradiol/Drospirenon 24+4 as a treatment of moderate acne vulgaris.

Table E5: Overview of methods to evaluate the primary efficacy parameters to support the indication of moderate acne vulgaris

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.
Percentage change in non-inflammatory lesions (open comedones and closed comedones)	
Percentage change in total lesions (inflammatory and non-inflammatory)	
Investigator Static Global Assessment (ISGA)	ISGA was obtained at screening and at each scheduled treatment visit.[1]

For all primary efficacy variables an FAS analysis and an amended FAS analysis were performed. The amended FAS analysis was considered to be the 'primary' analysis. The endpoint for efficacy analysis was visit 5 (day 17-24 of cycle 6), with missing values replaced by the last observed value carried forward. Percentage change from baseline in lesion count at a given visit is defined as (lesion count at visit – lesion count at baseline)*(100/lesion count at baseline).

Sample size determination

Two published reports[2,3] compared the efficacy of a triphasic, combination oral contraceptive (norgestimate-ethinylestradiol) to placebo for treatment of moderate acne. For these studies, the averages of the mean percent difference from baseline in lesion counts (baseline – cycle 6) * (100/baseline) for the Intent-to-Treat groups were, for inflammatory lesions: 47.80 for treatment and 30.26 for placebo (with a pooled SD of 50.16) and for total lesions: 41.74 for treatment and 27.52 for placebo (with a pooled SD of 39.02). A sample size of 250, assuming a dropout rate of 20%, would provide greater than 90% power to detect differences of these magnitudes. Assuming a common SD of 55 (the pooled SD for non-inflammatory lesions observed in these studies) and a 20% dropout rate, 90% power would be provided to detect a difference between treatment and placebo of 18.0 in non-inflammatory lesions. Assuming that 40 percent of the subjects in the active treatment group are classified as "clear" or "almost clear" on the ISGA, and a 20% dropout rate, this sample size would provide a lower greater than 90 to detect a difference of 16 percent or greater between active treatment and placebo.

A successful outcome for Ethinylestradiol/Drospirenon 24+4 in the treatment of moderate acne vulgaris was defined as:

- 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 (FDA response to Special Protocol Assessment; 12 Dec 2002).

- **Summary of primary endpoint results**
  Table E6 gives an overview of the results of the primary efficacy endpoint:

Table E6: Overview of primary efficacy variable results - amended FAS (pooled data of studies A25083 and A25152)

Amended FAS **DRSP/EE: 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**
	DRSP/EE: n=450 Placebo: n=442	DRSP/EE: n=450 Placebo: n=442	DRSP/EE: n=450 Placebo: n=442	DRSP/EE: n=451 Placebo: n=442
DRSP/EE versus 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. Ethinylestradiol/Drospirenon 24+4 (DRSP/EE) 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 center, 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 Ethinylestradiol/Drospirenon 24+4 and placebo groups. However, the reductions in all the counts were markedly greater in the Ethinylestradiol/Drospirenon 24+4 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.

[2] Redmond GP, Olson WH, Lippman JS, Kafrissen ME, Jones TM, Jorizzo JL. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: A randomized, placebo-controlled trial. Obstetrics and Gynecology 1997;89:615-22.
[3] Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M, Swinyer L. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. Journal of the American Academy of Dermatology 1997;37:746-54

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 endpoints chosen to evaluate efficacy of Ethinylestradiol/Drospirenon 24+4 in the treatment of moderate to severe acne vulgaris is considered adequate. Apart from lesion counts, the endpoint 'clear or almost clear' rating is considered a good addition to lesion count as it represents a very relevant clinical outcome from a patient's point of view. Combining these endpoints contributes to the overall picture of the efficacy of the preparation.
A significantly greater improvement versus placebo-treatment was noted both in lesion counts and in investigator 'clear' or 'almost clear' rating. The reduction in lesion counts achieved is comparable with that reported with other COC treatments and with different topical treatments (retinoids), including topical antibiotics, published in literature. A 'clear' to 'almost clear face' was achieved in up to 23% of patients after 6 months of treatment, which is lower than considered in the sample size considerations (40%), but the difference with placebo is nevertheless considered clinically relevant. Additionally, maximum improvement may not yet be reached at 6 months treatment for a chronic condition like acne, which is supported by the outcome as no plateau in efficacy endpoint was yet reached. This extra efficacy endpoint is not commonly used in published COC studies in acne treatment, so it is unclear whether this outcome is in line with other treatments.
In conclusion, the efficacy of Ethinylestradiol/Drospirenon 24+4 in the treatment of moderate to severe acne is considered adequately proven.

Clinical safety

Adverse drug reactions
The pattern of adverse drug reactions (ADRs) observed during treatment with Ethinylestradiol/Drospirenon 24+4 is considered typical for a combined oral contraceptive and did not deviate from that observed in the reference group treated with Mercilon®.

Venous thromboembolism
No cases of venous thromboembolism (VTE) were reported during the clinical development program of Ethinylestradiol/Drospirenon 24+4. As the exposure of Ethinylestradiol/Drospirenon 24+4-treated women was far too limited to adequately quantify the risk of rare events such as VTE, the incidence rates calculated for the marketed preparation Yasmin should be used as they are based on a larger database. It is agreed with the MAH that it may be safely assumed that Ethinylestradiol/Drospirenon 24+4, as a lower-dosed product, will not have a higher VTE risk as compared to Yasmin.

For the purpose of the safety assessment of DRSP-containing OCs with respect to the incidence of VTEs, all spontaneous VTE reports (event-based) received by the company by 31 October 2006 were included. These numbers include all confirmed VTEs regardless of whether the women had other significant risk factors in addition to OC use (e.g. obesity, coagulopathies, fractures, immobilization, surgery).
Since Yasmin was first launched in Europe in November 2000, a total of 749 VTEs had been spontaneously reported globally in association with DRSP-containing OCs. Currently, the cumulative spontaneous reporting rate of confirmed VTEs is 3.86 per 100,000 wy. The worldwide spontaneous reporting rates for pulmonary embolism (PE) was calculated to be 1.67 per 100,000 wy. Based on spontaneous reporting, the overall worldwide mortality rate related to VTEs among DRSP-containing OC users is 0.15 deaths per 100,000 wy.
These findings and the results of 3 post-marketing safety studies conducted with Yasmin to further assess the risks of SAEs, including the incidence of VTEs and arterial thromboembolic events (ATEs), beyond those data provided by the clinical development program, provide evidence that the VTE rate in Yasmin users is not increased compared to other OCs.
Specifically for Yasmin, the European Active Surveillance (EURAS) study compared the occurrence of rare clinical endpoints, such as VTE, among users of Yasmin, users of levonorgestrel containing OCs and users of all other OC in more than 58,000 OC users in 7 European countries (EURAS study, Dinger and Heinemann 2006, see section 2.7.4.6, Vol 14, pag 14). This recently completed 3-armed cohort study provided evidence that the VTE rate in Yasmin users is not increased compared to the VTE rate in users of other OCs.

However, the MAH has already initiated a similar active post-marketing surveillance program as for Yasmin: International Active Surveillance Study of Women Taking Oral Contraceptives (INAS OC, 11 Aug 2005) in order to provide early information and regular updates on relevant clinical outcomes which will contribute to a continuous risk – benefit assessment during long-term follow-up (3 to 5 years). This study is planned as a large, multinational, prospective, controlled, non-interventional, long-term cohort study that follows a series of cohorts. The cohorts consist of new users (first-ever users or switchers) of two different groups of OCs: OCs containing DRSP (Ethinylestradiol/Drospirenon 24+4 or Yasmin) and OCs containing other progestogens. The main clinical outcomes of interest for the short and long-term follow-up are: deep venous thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction and cerebrovascular accidents. It is planned to conduct recruitment of the cohort members via a network of approximately 1,000 OC prescribing physicians in the US and approximately 700 OC prescribing physicians in Europe. The combined cohort will include 50,000 women recruited in the US and Europe.

Pharmacovigilance System

The Pharmacovigilance system as described by the MAH fulfils the requirements and provides adequate evidence that the MAH has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Minimisation Plan

The INAS study will enable an estimate of the absolute risk of rare serious adverse outcomes to be made. This will contribute to a more continuous risk-benefit assessment in the long term.

Discussion on clinical aspects by the RMS

Efficacy in contraception

The relative benefit-risk of Ethinylestradiol/Drospirenon 24+4 in the indication of contraception can be considered positive.

With an overall Pearl Index for typical use (method + patient failure) of 0.80 (upper limit of 95% CI: 1.31) and a Pearl Index for method failure of 0.41 (upper limit of 95% CI: 0.85), the degree of contraceptive efficacy obtained with Ethinylestradiol/Drospirenon 24+4 falls within the range of that noted for other monophasic COCs.

The results obtained on percentage of withdrawal- and intercyclic bleeding in the comparative study versus Mercilon® did not indicate clear differences between groups, indicating that lengthening the treatment duration from 21 as in Yasminelle to 24 days per cycle in Ethinylestradiol/Drospirenon 24+4 did not have an unfavourable effect on the cycle control.

Efficacy in moderate to severe acne vulgaris

The selection of primary endpoints chosen to evaluate efficacy of Ethinylestradiol/Drospirenon 24+4 in the treatment of acne is considered adequate. Apart from lesion counts, the primary endpoint ‘clear or almost clear’ rating is considered a good addition to lesion count as it represents a very relevant clinical outcome from a patient’s point of view. Combining these endpoints contributes to the overall picture of the efficacy of the preparation. Both in lesion counts and in investigator ‘clear’ or ‘almost clear’ rating, a significantly greater improvement was noted. The reduction in lesion counts is comparable with that reported with other COC treatments and with different topical treatments including topical antibiotics published in literature. COCs and topical treatments appear to achieve highest reduction in inflammatory lesions, which pattern is also shown with the treatment of Ethinylestradiol/Drospirenon 24+4. A ‘clear’ to ‘almost clear face’ was achieved in up to 23% of patients after 6 months of treatment, which is lower than considered in the sample size considerations (40%), but the difference with placebo is nevertheless considered clinically relevant. Additionally, maximum improvement may not yet be reached at 6 months treatment for a chronic condition like acne, which is supported by the outcome as no plateau in efficacy endpoint was yet reached. This extra efficacy endpoint is not commonly used in published COC studies in acne treatment.

Clinical safety

The pattern of adverse drug reactions (ADRs) observed during treatment with Ethinylestradiol/Drospirenon 24+4 is considered typical for a combined oral contraceptive and did not deviate from that observed in the references group treated with Mercilon®.
Registration dossiers are too limited to adequately quantify the risk of rare events such as VTE. Nevertheless, the extensive post-marketing data that are available on the higher EE dosed Yasmin can serve as supportive documentation, which do not indicate a higher risk for VTE than observed for other COCs available on the market.
In order to anticipate on needs to quantify such rare events for Ethinylestradiol/Drospirenon 24+4, the MAH already initiated a similar active post-marketing surveillance program as for Yasmin: International Active Surveillance Study of Women Taking Oral Contraceptives (INAS OC, 11 Aug 2005) in order to provide early information and regular updates on relevant clinical outcomes which will contribute to a continuous risk-benefit assessment during long-term follow-up (3 to 5 years).

CMD(h) Referral
At the end of the MRP a number of CMSs did not consider the indication *treatment of moderate acne in women seeking oral contraception* approvable and therefore referred the procedure to the CMD(h). These CMSs only supported inclusion of clinical trial data on acne treatment in section 5.1 of the SmPC.
Although at the end of the CMD(h) referral all member states agreed that acne data for Ethinylestradiol/Drospirenon 24+4 are robust and the effect is clinically relevant, no agreement could be reached on the specific wording of this indication between all member states. The MAH therefore decided to remove the indication. The study results on acne vulgaris were included in section 5.1 of the SmPC.

Product information

SmPC
During the MRP, the MAH committed to harmonize SmPC section 4.4 (VTE statement) with the Yasmin SmPC. This commitment has been fulfilled through variation NL/H/1270/001/II/004. In addition, the MAH has modified the wording of SmPC section 5.1, concerning the description of the acne studies, as committed (variation NL/H/1270/001/II/002).

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot round followed by two rounds with 10 participants each. The test subjects were women of childbearing age (18 to 45 years), 50% of whom were or had been users of contraceptive pills.
The test included 14 questions on the text of the leaflet and 3 open questions regarding general impressions of the leaflet. These questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
There were sufficient questions about the critical sections. The questions addressed issues of importance for Ethinylestradiol/Drospirenon 24+4, being indication, dosing (missed pills), contraindications, warning section (in particular thrombosis, smoking and tumours) and side-effects.
In the first round of testing all questions were located and answered correctly by at least 81% of the subjects. Therefore no changes were made to the leaflet prior to the second round of testing. In the second round again all questions were located and answered correctly by at least 81% of the subjects, except for question 4. Question 4 was located by 8 out of 10 subjects in round two, however, in the overall results 17 out of 20 subjects located this question. Therefore there was no need to adapt the leaflet.

Based on the general impressions of the participants, the main issue with the leaflet is its length. As expected some subjects experienced difficulty in locating the information. All subjects appeared to make use of the table of contents. Due to the length of the booklet, the time taken to locate the information and provide the answers is not unreasonable. The table of contents was considered very helpful by most subjects. Overall, readability of the leaflet has been demonstrated. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The chemical-pharmaceutical information about the manufacturing, the quality requirements with regard to the substances and the finished product are sufficient within the framework of the European registration requirements.

The MAH applied for two indications: *oral contraception* and *treatment of moderate acne vulgaris in women seeking oral contraception*.

The overall Pearl Index for typical use (method + patient failure) is 0.80 with an upper limit of the two-sided 95% CI of 1.30, while the PIc (method failure) is 0.41 with an upper two-sided 95% confidence limit of 0.85 showing that the degree of contraceptive efficacy obtained with Ethinylestradiol/Drospirenon 24+4 falls well within the range of that noted for other monophasic COCs.

The pattern of adverse drug reactions (ADRs) observed during treatment with Ethinylestradiol/Drospirenon 24+4 is considered typical for a combined oral contraceptive and did not deviate from that observed in the reference group treated with Mercilon.
Registration dossiers are too limited to adequately quantify the risk of rare events such as VTE. Nevertheless, the extensive post-marketing data that are available on the higher EE dosed Yasmin can serve as supportive documentation, which do not indicate a higher risk for VTE than observed for other COCs available on the market. The initiative for an active post-marketing surveillance program (INAS study) is therefore supported.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SmPC, package leaflet and labelling are in the agreed templates and are in agreement with similar products.

The MEB, on the basis of the data submitted, considered that Ethinylestradiol/Drospirenon 24+4 0.02 mg/3 mg Berlipharm, film-coated tablets demonstrated adequate evidence of efficacy as well as a satisfactory risk/benefit profile for the indications *oral contraception* and *treatment of moderate acne vulgaris in women seeking oral contraception* and granted a marketing authorisation. Ethinylestradiol/Drospirenon 24+4 0.02 mg/3 mg Berlipharm, film-coated tablets was authorised in the Netherlands on 11 October 2007.

The national registration in the Netherlands was followed by MRP NL/H/1270/001/MR, which started on 30 November 2007. The concerned member states mutually recognised the Dutch evaluation for the indication *oral contraception*. However, by the end of the MRP, several CMSs expressed their disapproval of the proposed indication *treatment of moderate to severe acne vulgaris in women seeking oral contraception*. As consensus could not be reached on this issue, a CMD(h) referral was initiated on 29 February 2008.

During the CMD(h) referral, the MAH provided additional information to support the proposed indication. The acne indication was discussed again in the Board meeting of 17 April 2008. The Board followed the advice of the assessors and maintained its positive position on inclusion of this indication.
Although at the end of the CMD(h) referral all member states agreed that acne data for Ethinylestradiol/Drospirenon 24+4 are robust and the effect is clinically relevant, no agreement could be reached on the specific wording of the acne indication between all member states. The MAH therefore decided to pursue only the application for the indication *oral contraception*. However, the member states did agree to include clinical trial data on acne treatment in section 5.1 of the SmPC. The mutual recognition procedure was finished on 29 April 2008.

The PSUR submission cycle is 3 years. The first PSUR for Yasmin, Yasminelle and Ethinylestradiol/Drospirenon 24+4 covers the period from September 2006 to September 2009.

The date for the first renewal will be 29 June 2012.

The following post-approval commitments have been made during the procedure:

Quality - active substance
- The MAH committed to submit a variation for the updated manufacturing process for the active substance drospirenone. This commitment has been fulfilled through NL/H/1270/001/II/001.

Environmental risk
- The MAH committed to complete the Environmental Risk Assessment with the submission of the respective risk assessment report to the European Health Authorities. This commitment has been partially fulfilled (NL/H/1270/001/II/014).

SmPC
- The MAH committed to harmonize SmPC section 4.4 (VTE statement) with the Yasmin SmPC. Upon conclusion of the Yasmin variation, harmonization for Ethinylestradiol/Drospirenon 24+4 will be sought if the outcome for the general text should differ. This commitment has been fulfilled (NL/H/1270/001/II/004).
- The MAH committed to submit a Type II SmPC variation within 60 days to resolve remaining issues on section 5.1 This commitment has been fulfilled (NL/H/1270/001/II/002).

Pharmacovigilance
- A post-marketing surveillance study, the INAS study, is already running in the USA. As outlined in the EU-Risk-Management-Plan, this study will be extended to the EU markets upon approval and launch of Ethinylestradiol/Drospirenon 24+4. The MAH committed to report interim results at regular intervals.

List of abbreviations

ADR	Adverse Drug Reaction
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMSs	Concerned Member State(s)
COC	Combined Oral Contraceptive
CV	Coefficient of Variation
DHEA-S	Dehydroepiandrosterone sulphate
DRSP	Drospirenone
DVT	Deep Venous Thrombosis
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EE	Ethinylestradiol
EU	European Union
FAS	Full analysis set
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCG	Human Chorionic Gonadotropin
ICH	International Conference of Harmonisation
ISGA	Investigator Static Global assessment
LOCF	Last Observation Carried Forward
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MRP	Mutual Recognition Procedure
NF	National Formulary
NNT	Number Needed to Treat
OC	Oral Contraceptive
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PE	Pulmonary Embolism
Ph.Eur.	European Pharmacopoeia
PI	Pearl Index
PIL	Package Leaflet
PMDD	Premenstrual Dysphoric Disorder
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
RMS	Reference Member State
SD	Standard Deviation
SHBG	Sex-Hormone-Binding Globuline
SmPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
VTE	Venous Thromboembolism

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in synthesis of the drug substance drospirenone.	NL/H/1270/ 001/II/001	II	10-7-2008	4-8-2008	Approval	N
Modified wording in SmPC, section 5.1: Description of the acne studies.	NL/H/1270/ 001/II/002	II	24-7-2008	22-9-2008	Approval	N
To add the indication "Treatment of emotional and physical symptoms of Premenstrual Dysphoric Disorder in women seeking oral contraception".	NL/H/1270/ 001/II/003	II	26-8-2008	10-2-2010	Withdrawn	Y, Annex I
Update of product information (SmPC sections 4.2, 4.4, 4.5, 4.8 and 5.1 and PIL).	NL/H/1270/ 001/II/004	II	11-9-2008	7-5-2009	Approval	N
Change in the manufacturer of the active substance or starting material/reagent/intermediate in the manufacturing process of the active substance where no Ph.Eur. Certificate of Suitability is available; new manufacturer (replacement or addition).	NL/H/1270/ 001/IB/005	IB	9-1-2009	8-2-2009	Approval	N
To add the indication "Treatment of moderate acne vulgaris only in women seeking oral contraception".	NL/H/1270/ 001/II/006	II	11-2-2009	6-7-2012	Non-approval	Y, Annex II
Change in the specification of the finished product; tightening of specification limits.	NL/H/1270/ 001/IB/007	IB	16-7-2009	15-8-2009	Approval	N
Change in test procedure of the finished product; other changes to a test procedure; including replacement or addition of a test procedure.	NL/H/1270/ 001/IB/008	IB	15-7-2009	14-8-2009	Approval	N
Change in the specification of the finished product; tightening of specification limits.	NL/H/1270/ 001/IB/009	IB	16-7-2009	15-8-2009	Approval	N
Change in test procedure of the finished product; other changes to a test procedure; including replacement or addition of a test procedure.	NL/H/1270/ 001/IB/010	IB	15-7-2009	14-8-2009	Approval	N
Change in the name and/or address of the MAH in BE and FR.	NL/H/1270/ 001/IA/011	IA	26-8-2009	9-9-2009	Approval	N
Change in shape or dimensions of the container or closure	NL/H/1270/ 001/IA/012	IA	6-1-2010	20-1-2010	Approval	N
Change in the name of the medicinal product in all member states except CZ and UK	NL/H/1270/ 001/1B/013	IB	13-11-2009	08-02-2010	Approval	N
Post-approval commitment - updated Environmental Risk Assessment report.	NL/H/1270/ 001/II/014	II	18-1-2010	20-10-2010	Approval	N
Update of Detailed Description of Pharmacovigilance System.	NL/H/1270/ 001/II/015	II	25-3-2010	16-4-2010	Approval	N
Update of product information (SmPC sections 4.4 and 5.1 and PIL).	NL/H/1270/ 001/WS/ 016	WS (II)	27-5-2010	26-10-2012	Approval	N
Replacement or addition of a manufacturer responsible for batch release not including batch control/testing	NL/H/1270/ 001/IB/017	IA	14-8-2010	13-9-2010	Approval	N
Changes to an existing pharmacovigilance system as described in the DDPS.	NL/H/1270/ 001/IA/018/ G	IA/G	25-8-2010	24-9-2010	Approval	N
Implementation of change(s) requested by the EMEA/ National	NL/H/1270/ 001/IB/019	IB	3-9-2010	3-10-2010	Approval	N

Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SmPC.						
Changes to the Pharmacovigilance system.	NL/H/1270/001/IA/020/G	IA/G	28-1-2011	27-2-2011	Approval	N
MAH name change in FI.	NL/H/1270/001/IA/021	IA	28-1-2011	27-2-2011	Approval	N
MAH address change in SK.	NL/H/1270/001/IA/022/G	IA/G	2-3-2011	1-4-2011	Approval	N
Changes to section 4.8 of the SmPC.	NL/H/1270/001/II/023	II	5-6-2011	25-11-2011	Withdrawn	N
Tightening of specification limits, additions of a new specification parameter to the specification with its corresponding test method, updated certificate from an already approved manufacturer.	NL/H/1270/001/IA/024/G	IA/G	14-6-2011	14-7-2011	Approval	N
Implementation of agreed wording changes for which no data are submitted by the MAH.	NL/H/1270/001/IB/025	IB	25-5-2011	8-6-2011	Approval	N
Change in the name and/or address of the marketing authorisation holder; change in the name and/or address of a manufacturer of the finished product, including quality control sites, manufacturer responsible for batch release.	NL/H/1270/001/IA/026/G	IA/G	26-7-2011	25-8-2011	Rejected	N
Change in the name and/or address of the marketing authorisation holder; change in the name and/or address of a manufacturer of the finished product, including quality control sites, manufacturer responsible for batch release.	NL/H/1270/001/IA/027/G	IA/G	11-11-2011	11-12-2011	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products; Replacement or addition of a site where batch control/testing takes place	NL/H/1270/001/IB/028/G	IB/G	1-12-2011	31-12-2011	Approval	N
Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DDPS. Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system Change of employed Clinical Research Organisations (CRO) for case processing and evaluation services. Another CRO is added for review, retrieval and extraction of data from medical and legal	NL/H/1270/001/IA/029/G		16-5-2012	15-6-2012	Approval	N

documents. Update to reflect the name change of Bayer. Update to reflect organisational changes within the company; esp. adaptation to current GPV organization: The PV Systems Group was organizationally moved from “Single Case Processing” to “Quality Training and Compliance” and became system owner of the database.						
Update of product information SmPC section 4.2: to extend the time window for missed pills from 12h to 24h in line with the EE/DRSP phase 3 study protocols and PIL.	NL/H/1270/001/II/030	II	16-8-2012	9-1-2013	Approval	N
New CEP for the drug substance drospirenone from an already approved manufacturer.	NL/H/1270/001/IA/031/G	IA/G	16-10-2012	15-11-2012	Approval	N
Removal of the contraindication "pancreatitis or a history thereof if associated with severe hypertriglyceridemia" from section 4.3 of the SmPC and section 2 of the PL while maintaining the corresponding statement in the precautions/warnings sections	NL/H/1270/001/WS/032	WS (II)	24-1-2013	25-3-2013	Approval	N
Introduction of the PSMF.	NL/H/1270/001/IA/033/G	IA/G	15-2-2013	17-3-2013	Approval	N
Replacement of the CEP for the starting material betadex of a new manufacturer. The new certificate of suitability replaces the former one. Change in batch size of the drug product drospirenone + ethinyl-estradiol coated tablet 3 mg + 20 µg . Minor change in the manufacturing process.	NL/H/1270/001/IA/034/G	IA/G	28-6-2013	28-7-2013	Approval	N

ANNEX I – Submitted variation for addition of indication *Treatment of emotional and physical symptoms of Premenstrual Dysphoric Disorder in women seeking oral contraception* (NL/H/1270/001/II/003)

I RECOMMENDATION

Based on the review of the data on safety and efficacy, the type II variation for Ethinylestradiol/ Drospirenon 24+4 Berlipharm for addition of the indication *Treatment of emotional and physical symptoms of PMDD (Premenstrual Dysphoric Disorder) only in women seeking oral contraception. The effectiveness of Ethinylestradiol/Drospirenon 24+4 for PMDD when used for more than three menstrual cycles has not been evaluated*, is considered not approvable.

This conclusion was agreed by the RMS and concerned member states. However, at the end of the variation procedure no agreement could be reached between the member states on the inclusion of the clinical study results in the SmPC in the absence of a therapeutic indication. The procedure was subsequently referred to the CHMP for arbitration in July 2009, followed by the MAH's decision to withdraw the application on 10 February 2010.

II EXECUTIVE SUMMARY

II.1 Introduction

For the sought PMDD indication, the same dosage regimen is proposed as for the indication *'Oral contraception'.* In addition, the MAH proposed to add information relating to use in PMDD to section 4.4 of the SmPC, a second table with adverse drug reactions in section 4.8, and two paragraphs regarding efficacy results in the indication of PMDD in section 5.1.

In the USA, the indication PMDD was granted in October 2006. The labelling in the USA indicates the following in section 'Indications and usage':
Ethinylestradiol/Drospirenon 24+4 is also indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of Ethinylestradiol/Drospirenon 24+4 for PMDD when used for more than 3 menstrual cycles has not been evaluated.
The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses; the disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.
Ethinylestradiol/Drospirenon 24+4 has not been evaluated for the treatment of premenstrual syndrome (PMS).

PMDD as clinical diagnosis
The handbook of the American Psychiatric Association is the Diagnostic and Statistical Manual of Mental Disorders (DSM). In 1994, PMDD was classified as "depressive disorder not otherwise specified" and

emphasized emotional and cognitive-behavioural symptoms[4]. At least five of the 11 specified symptoms must be present for a diagnosis of PMDD (table 1). These symptoms should be limited to the luteal phase and should not represent amplification of pre-existing depression, anxiety, or personality disorder. In addition, they must be confirmed prospectively by daily rating for at least two consecutive menstrual cycles. At the time of the assessment it was unsure how PMDD would be included in the 2012 edition of the DSM (DSM-V).

TABLE 1
Research Criteria for Premenstrual Dysphoric Disorder

A. In most menstrual cycles during the past year, five (or more) of the following symptoms were present for most of the time during the last week of the luteal phase, began to remit within a few days after the onset of the follicular phase, and were absent in the week postmenses, with at least one of the symptoms being either (1), (2), (3), or (4):
   1. Markedly depressed mood, feelings of hopelessness, or self-deprecating thoughts
   2. Marked anxiety, tension, feelings of being "keyed up" or "on edge"
   3. Marked affective lability (e.g., feeling suddenly sad or tearful or increased sensitivity to rejection)
   4. Persistent and marked anger or irritability or increased interpersonal conflicts
   5. Decreased interest in usual activities (e.g., work, school, friends, hobbies)
   6. Subjective sense of difficulty in concentrating
   7. Lethargy, easy fatigability, or marked lack of energy
   8. Marked change in appetite, overeating, or specific food cravings
   9. Hypersomnia or insomnia
   10. A subjective sense of being overwhelmed or out of control
   11. Other physical symptoms, such as breast tenderness or swelling, headaches, joint or muscle pain, a sensation of "bloating," or weight gain

B. The disturbance markedly interferes with work or school or with usual social activities and relationships with others (e.g., avoidance of social activities, decreased productivity and efficiency at work or school).

C. The disturbance is not merely an exacerbation of the symptoms of another disorder, such as major depressive disorder, panic disorder, dysthymic disorder, or a personality disorder (although it may be superimposed on any of these disorders).

D. Criteria A, B, and C must be confirmed by prospective daily ratings during at least two consecutive symptomatic cycles. (The diagnosis may be made provisionally prior to this confirmation.)

NOTE: *In menstruating females, the luteal phase corresponds to the period between ovulation and the onset of menses, and the follicular phase begins with menses. In nonmenstruating females (e.g., those who have had a hysterectomy), the timing of luteal and follicular phases may require measurement of circulating reproductive hormones.*

Regulatory history of PMDD

In 1998, a panel of experts supported by Eli Lilly evaluated the evidence then available, and a consensus was reached that PMDD was a distinct clinical entity. Although not unanimously accepted by those present, the positive response was presented to regulatory agencies[5]. Subsequently, in 1999, the FDA Neuropharmacology Advisory Committee supported this concept. There are now four prescription drugs that have been approved by the FDA for treating PMDD. These FDA-approved medications are fluoxetine (Sarafem), paroxetine controlled-release (Paxil CR), and sertraline (Zoloft), together with the drospirenone/ethinylestradiol oral contraceptive (Ethinylestradiol/Drospirenon 24+4).

[4] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, D.C.: American Psychiatric Association, 1994:715-8.
[5] Endicott J, Amsterdam J, Eriksson E et al. Is premenstrual dysphoric disorder a distinct clinical entity? J Womens Health Gend Based Med 1999;8:663-679.

The Medicines Control Agency in the UK also recognised in 1999 the existence of PMDD and approved fluoxetine as a treatment for it. In 2003 though, the license for fluoxetine to treat PMDD in four EU countries was recalled in the Article 30 referral procedure EMEA/CPMP/3263/03 on the grounds that *"PMDD is not a well-established disease entity across Europe. It is not listed in the International Classification of Diseases (ICD) and remains only a research diagnosis in DSM-IV. There was considerable concern that women with less severe pre-menstrual symptoms might erroneously receive a diagnosis of PMDD resulting in widespread inappropriate short and long-term use of fluoxetine"*[6]. Nevertheless, the submitted two pivotal trials were robust enough to be included under section 5.1 Pharmacodynamic properties of the harmonised SmPC of fluoxetine.

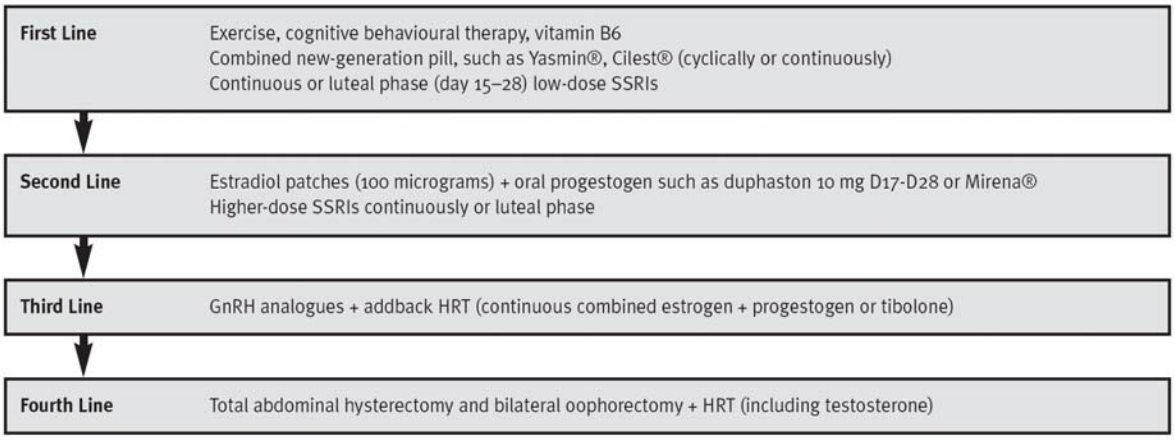
Treatment of PMDD

USA
In the USA, the SSRI's are the first-line treatment of choice for severe PMDD. Fluoxetine, paroxetine and sertraline are approved by the FDA during luteal phase, as well as continuous administration. Further, the combined oral contraceptive Ethinylestradiol/Drospirenon 24+4 is approved for this indication.

Europe
Although currently no medicinal products are approved in Europe for PMDD, in the harmonised SmPC for fluoxetine-containing medicinal products - including Prozac - two placebo controlled trials are described in section 5.1 in patients meeting PMDD diagnostic criteria according to DSM-IV.
Moreover, several gynaecological associations have treatment guidelines for PMDD:

- The guideline regarding premenstrual syndrome of the Dutch Association of Obstetrics and Gynaecology (NVOG)[7] states that, efficacy has been proven for gonadotropin-releasing hormone (GnRH) agonists and SSRI's in the treatment of PMS/PMDD, and can be considered for treatment of PMDD.
- The guideline of the UK Royal College of Obstetricians and Gynaecologists of December 2007 (figure below) recognizes the clinical need for medication for PMS/PMDD[8].

Figure: Possible treatment regimen for the management of severe PMS/PMDD. Adopted from RCOG.



Spironolactone
Spironolactone is an aldosterone receptor antagonist used as a diuretic and antihypertensive. In the off-license treatment of PMS/PMDD it has been shown to improve physical and mood symptoms compared to

[6] Committee for proprietary medicinal products (CPMP), Summary information on referral opinion following arbitration pursuant to Article 30 of council directive 2001/83/EC for Prozac and associated names. EMEA/CPMP/3263/03.
[7] Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG). Guideline No. 19 "Het premenstrueel syndroom". January 1999.
[8] Royal College of Obstetricians and Gynaecologists (RCOG). Green-top Guideline No. 48 "Management of premenstrual syndrome". December 2007.

placebo[9,10]. In contrast, Vellacott et al.[11] reported that mood symptoms were not significantly improved with spironolactone compared with placebo. Some controversy thus still exists over spironolactone as a treatment for PMS/PMDD.
The synthetic progestagen drospirenone, present in Ethinylestradiol/Drospirenon 24+4, is an analog to spironolactone. The MAH claims that the antimineralocorticoid properties may be especially beneficial in relieving physical symptoms. In addition, the antiandrogenic properties may positively affect the mood of women with PMDD.

III SCIENTIFIC DISCUSSION

III.1 Clinical aspects

The clinical documentation in support of this type II variation consisted of 1 Phase III parallel study (A21566) and 1 Phase III cross-over study (A07545). Both phase III studies were conducted in the USA and are published in international, peer-reviewed journals.[12,13] Only the pivotal study A21566 will be discussed in detail in this public assessment report. Please note that Yaz in these studies represents Ethinylestradiol/Drospirenon 24+4 Berlipharm.

TT 1 Overview of clinical phase 3 studies evaluating the efficacy of YAZ in the treatment of PMDD

Study no. (Protocol no.)	Study Type Phase	Study Design	Study medication	Duration of treatment (regimen)	Number of women treated [c]	Age range (mean)
A21566 (304049)	Efficacy/Safety Phase 3	Multicenter, randomized, double-blind, placebo-controlled, **parallel group**	YAZ Placebo	3 cycles (24-day regimen)	231 218	18-40 years (31.0 years) 18-42 years (32.0 years)
A07545 (305141)	Efficacy/Safety Phase 3	Multicenter, randomized, double-blind, placebo-controlled, **crossover**	YAZ; Placebo [a] Placebo; YAZ [b]	6 cycles (24-day regimen), 3 cycles per treatment	34 30	19-39 years (31.9 years) 20-40 years (31.8 years)

[a] Treatment group first received YAZ for 3 treatment cycles, then no study medication for 1 cycle, and then placebo for 3 treatment cycles.
[b] Treatment group first received placebo for 3 treatment cycles, then no study medication for 1 cycle, and then YAZ for 3 treatment cycles.
[c] numbers refer to the full analysis set (FAS)

[9] Wang M, Hammarbäck S, Lindhe BA et al. Treatment of premenstrual syndrome by spironolactone: a double-blind, placebo-controlled study. Acta Obstet Gynecol Scand 1995;74:803-8.
[10] Hellberg D, Claesson B, Nilsson S. Premenstrual tension: a placebo-controlled efficacy study with spironolactone and medroxyprogesterone acetate. Int J Gynaecol Obstet 1991;34:243-8.
[11] Vellacott ID, Shroff NE, Pearce MY, et al. A double-blind, placebo-controlled evaluation of spironolactone in the premenstrual syndrome. Curr Med Res Opin 1987;10:450-6.
[12] Yonkers KA, Brown C, Pearlstein TB et al. Efficacy of a new low-dose oral contraceptive with drospirenone in premenstrual dysphoric disorder. Obstet Gynecol 2005;106:492-501.
[13] Pearlstein TB, Bachmann GA, Zacur HA et al. Treatment of premenstrual dysphoric disorder with a new drospirenone-containing oral contraceptive formulation. Contraception 2005;72:414-21.

III.1.1 Main phase III study A21566

III.1.1.1 Design

Study A21566 was a multicenter, double-blind, randomized, placebo-controlled, parallel group study. A total of 449 otherwise healthy women of reproductive age who had a diagnosis of PMDD were included and randomized to the Ethinylestradiol/Drospirenon 24+4 Berlipharm or placebo group. The study was composed of 2 phases: the qualification phase consisted of 2 run-in (menstrual) cycles, and the treatment phase consisted of 3 treatment cycles with Ethinylestradiol/Drospirenon 24+4 or placebo.

Treatments
DRSP 3 mg/EE 20 µg tablets were orally administered during the treatment period to subjects randomized to the active treatment group. The dosing regimen was as follows: Day 1 - 24 DRSP 3 mg/EE 20 µg tablets and Day 25 - 28 inert tablets.
Identical placebo tablets were orally administered during the treatment period to subjects randomized to the placebo group. The dosing regimen was as follows: Day 1 - 24 placebo tablets matching the active DRSP/EE tablets and Day 25 - 28 inert tablets.

Study participants

The inclusion criteria were:
1. Between 18 and 40 years of age (inclusive), smokers maximum age of 34 at inclusion (Prior to protocol amendment 4, the maximum age of smokers was 30 years.)
2. PMDD according to DSM-IV criteria
   - At screening by history
   - At end of the second run-in cycle by review of symptom records
4. No oral contraceptives for at least 3 months prior to study entry.
5. Regular menstrual cycles (25-34 days).

PMDD severity criteria included:
6. a premenstrual-phase (days -5 to -1 before bleeding) daily average of 3.5 or greater for 5 distinct items in the DRSP (Daily Record of Severity of Problems) (Protocol amendment 1, changes were made as this was too restrictive, based on pilot data: premenstrual-phase (days -5 to -1 before bleeding) daily average of 3.0 or greater for 5 distinct items in the DRSP.)
7. a premenstrual-phase daily average that was twice as high as the corresponding postmenstrual phase average for the 5 distinct items.
8. a postmenstrual phase (days 6-10) daily average of 2.5 or less for each of the 11 distinct items in the DRSP.
9. a score of 3 or greater on one DRSP functional impairment item (items 22-24, table 1) for at least 2 luteal days.

The exclusion criteria were:
10. Depressive, anxiety, eating, bipolar, psychotic, somatoform, dysthymic, or drug/alcohol use disorders during the last 2 years.
11. Contraindication to oral contraceptive pill treatment.
12. Any formal psychotherapeutic counseling within 1 month before screening visit 1 or used medication for PMS or PMDD including, but not limited to hormones, bromocriptine, GnRH agonists, vitamin B6 (> 100 mg), calcium supplements (> 1500 mg/day), anxiolytics, and antidepressants during the 3-month period prior to screening visit 1.

Outcomes/endpoints

Primary efficacy variable
DRSP-scale (Daily Record of Severity of Problems) – DRSP sum score based on the first 21 of the 24 items was the primary efficacy variable. The primary efficacy endpoint of the study was the change in the average of the DRSP sum scores during the last five days before menses of the three treatment cycles,

compared with the average DRSP sum scores of the last five days before menses of the two baseline run-in cycles. This endpoint was compared between treatment (Ethinylestradiol/Drospirenon 24+4) and placebo groups.

Daily Record of Severity of Problems (DRSP) scale
In both Phase III studies, the DRSP scale was used to define the primary endpoint and was also part of the secondary efficacy variables. The DRSP has been used for measuring response to treatment of PMDD symptoms. The DRSP was developed to aid clinicians in the assessment of the DMS-IV criteria for PMDD as well as to assess severity of symptoms and impairment at various phases of the menstrual cycle. This daily questionnaire has been used in several trials in public literature[14,15]. As a sum score of the questionnaire it is usual to take the first 21 items. The DRSP is a validated questionnaire[16]. Endicott et al. 2006 showed that items and sum scores are sensitive to change and to treatment differences. The RCOG is of the opinion that the DRSP is well-established and simple for patients to use[17]. The RMS concluded that the use of the DRSP as the primary efficacy variable is acceptable, since it is validated and its usefulness is well established.

The scale consists of 11 distinct items (table 1, criteria A and table TT2) and 3 functional impairment items (table 1, criteria B and table TT2). These additional three items cover different types of functional impairment to record the degree of interference with daily life. The 11 emotional and physical distinct items consist of 21 individual items.
Each of the items is rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum sum score of 126 is possible on the first 21 items.

[14] Sternfeld B, Swindle R, Chawla A, et al. Severity of premenstrual symptoms in a health maintenance organziation population. Obstet Gynecol 2002;99:1014-24.
[15] Cohen LS, Miner C, Brown E et al. Premenstrual daily fluoxetine for premenstrual dysphoric disorder: A placebo-controlled, clinical trial using computerized diaries. Obstet Gynecol 2002;100:435-44.
[16] Endicott J, Nee J and Harrison W. Daily Record of Severity of Problems (DRSP): reliability and validity. Arch Womens Ment Health 2006;9:41-9.
[17] Royal College of Obstetricians and Gynaecologists (RCOG). Green-top Guideline No. 48 “Management of premenstrual syndrome”. December 2007.

TT 2 Daily Record of Severity of Problems: psychological/physical and functional impairment items

Distinct items	PMDD symptoms from DSM-IV	Individual items (symptoms)	Physical items	Mood items
Psychological/physical items				
1a*	Felt depressed, sad, 'down,' or 'blue'	1		+
1b*	Felt hopeless	2		+
1c*	Felt worthless or guilty	3		+
2*	Felt anxious, tense, 'keyed up' or 'on edge'	4		+
3a*	Had mood swings (e.g. suddenly felt sad or tearful)	5		+
3b*	Was more sensitive to rejection or my feelings were easily hurt	6		+
4a*	Felt angry, irritable	7		+
4b*	Had conflicts or problems with people	8		+
5	Had less interest in usual activities e.g. work, school, friends, hobbies)	9		
6	Had difficulty concentrating	10		
7	Felt lethargic, tired, fatigued, or had a lack of energy	11	+	
8a	Had increased appetite or overate	12	+	
8b	Had cravings for specific foods	13		
9a	Slept more, took naps, found it hard to get up when intended	14		
9b	Had trouble getting to sleep or staying asleep	15	+	
10a	Felt overwhelmed or that I could not cope	16		+
10b	Felt out of control	17		+
11a	Had breast tenderness	18	+	
11b	Had breast swelling, felt 'bloated,' or had weight gain	19	+	
11c	Had headache	20	+	
11d	Had joint or muscle pain	21	+	
Functional impairment items				
1	At work, at school, at home, or in daily routine, at least one of the problems noted above caused reduction of productivity or inefficiency	22		
2	At least one of the problems noted above interfered with hobbies or social activities (e.g. avoid or do less)	23		
3	At least one of the problems noted above interfered with relationships with others	24		

* items characterized as core symptom

Secondary efficacy variables

The RMS considers the following endpoints the most important secondary endpoints:

1) The difference of the average of the 3 treatment cycle scores from the baseline score for that period for the 3 individual items 22 to 24 (item 22 describing reduction of productivity at work,

home, or school; item 23 describing interference with hobbies or social activities; and item 24 describing interference with relationships).

2) The following variables from the Clinical Global Impressions (CGI):
- change from baseline in severity of illness score (observer-rated);
- efficacy index score (observer-rated);
- global improvement score (observer- and self-rated);
- the number of responders according to the efficacy index.

The items 22-24 of the DRSP questionnaire describe specific types of impairment in functioning. It is important to not only show a decrease in symptoms (assessed in the first 21 items of the DRSP – primary endpoint), but also an improvement in impairment. Therefore, these 3 individual items are all considered important secondary efficacy measures by the RMS. Further, the CGI global improvement score (observer-rated) was also considered of importance as a secondary efficacy measure.

III.1.1.2 Results

Primary efficacy analysis
The baseline values for the full analysis set were 77.4 and 78.1 for Ethinylestradiol/Drospirenon 24+4 and Placebo, respectively (Text Table 9 and table TF1).

Text Table 9: Descriptive Statistics for Baseline and DRSP Scores (First 21 Items) by Treatment Group and Period (Full Analysis Set)

		Treatment Group	
		DRSP/EE	Placebo
Period		N = 231	N = 218
Baseline [a]	n	190	194 [b]
	Mean ± SD	77.401 ± 16.698	78.075 ± 17.766
	Median	75.150	76.450
	Minimum – Maximum	46.80 – 126.00	29.20 – 124.50
Average of treatment cycles [c]	n	190	195
	Mean ± SD	41.18 ± 17.442	48.08 ± 21.129
	Median	35.70	42.67
	Minimum - Maximum	21.0 – 115.4	21.0 – 118.0

[a] Baseline is the average of the 2 run-in cycles scores.
[b] Subject 450004 had no baseline DRSP score.
[c] Average of treatment cycles score is the average of the DRSP cycle scores from treatment cycles 1 to 3.
DRSP/EE = drospirenone 3 mg/ethinyl estradiol 20 µg; DRSP score = Daily Record of Severity of Problems score; SD = standard deviation.
Reference: Table 15 and Table 16.

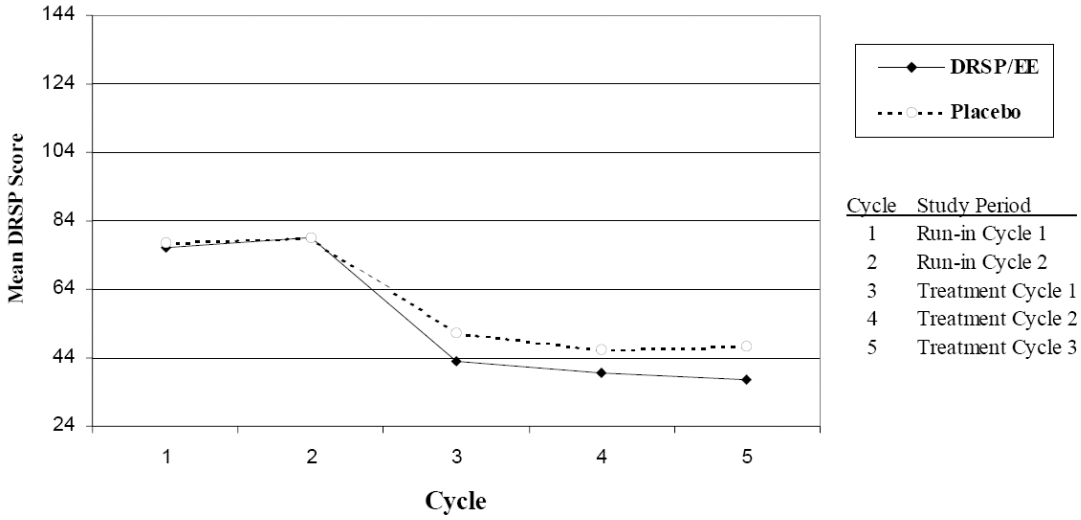
The results for the full analysis set demonstrated that the model-estimated mean change from baseline in the DRSP score was –37.5 while under treatment with Ethinylestradiol/Drospirenon 24+4 and –30.0 while under treatment with placebo. The difference (-7.5) was statistically significant (p = 0.0001). Likewise, the difference found in the per protocol analysis set (-8.9) was also statistically significant (p < 0.0001).

	Change from Baseline (n)		Difference (95% CIs)
	DRSP/EE (N=231)	Placebo (N=218)	
Full analysis set	-37.5 (190)	-30.0 (194)	-7.5 (-11.2, -3.8)
Per protocol analysis set	-38.1 (158)	-29.3 (166)	-8.9 (-12.9, -4.8)

N = total number of women in treatment group; n = total number of women with available data

The mean Daily Record of Severity of Problems scores by treatment and cycle is graphically presented in figure TF1 where cycles 1 and 2 are the run-in cycles, and cycles 3 to 5 are treatment cycles 1 to 3.

TF 1 Mean Daily Record of Severity of Problems scores (first 21 individual items) by treatment group and cycle - FAS (study A21566)



Responders

A response was defined as a reduction of 50% on the Daily Record of Severity of Problems sum score (primary endpoint). The response to Ethinylestradiol/Drospirenon 24+4 was 48.4%, whereas the placebo response was 36.1%.

	DRSP/EE (N=190)	Placebo (N=194)	Difference (DRSP/EE minus placebo)
Parallel study A25166	48.4% 92 responders	36.1% 70 responders	12.3%

Main secondary efficacy analyses

The results for the secondary endpoints, considered most important by the RMS, are depicted below.

	Baseline[a] (n)		Change from Baseline (n)		Difference (95% CIs)	Scale
Secondary endpoints	DRSP/EE (N=231)	Placebo (N=218)	DRSP/EE (N=231)	Placebo (N=218)		
Item 22 – Reduction of productivity or inefficiency at work, home or school	3.89 ± 0.92 (189)	3.94 ± 1.00 (194)	-1.98 (189)	-1.64 (194)	-0.33 (-0.55, -0.12) (p = 0.0022)	rated as 1 (not at all) to 6 (extreme)
Item 23 – Interference with hobbies or social activities	3.75 ± 1.06 (189)	3.83 ± 1.08 (194)	-1.94 (189)	-1.61 (194)	-0.34 (-0.55, -0.12) (p = 0.0020)	rated as 1 (not at all) to 6 (extreme)
Item 24 – Interference with relationships	3.95 ± 1.00 (189)	4.14 ± 0.94 (194)	-2.10 (189)	-1.68 (194)	-0.42 (-0.64, -0.20) (p=0.0002)	rated as 1 (not at all) to 6 (extreme)

N = total number of women in treatment group; n = total number of women with available data; [a] Baseline is the average of the 2 run-in cycles

		Treatment cycles			Adjusted mean	Difference (95% CIs)	Scale
Secondary endpoint		Mean cycle 1	Mean cycle 2	Mean cycle 3			
CGI – Global	DRSP/EE (231)	2.4 (181)	2.0 (159)	1.9 (161)	2.21 (212)	0.30 (-0.55, -0.047) (p=0.020)	rated as 1 (very much

Improvement	Placebo (218)	2.9 (181)	2.5 (164)	2.5 (161)	2.51 (198)	--	improved) to 7 (very much worse)

IV UPDATED DISCUSSION, OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

IV.1 Benefit-risk assessment of the RMS

The RMS concluded that the amount of clinical evidence in support of the treatment of emotional and physical symptoms of PMDD is considered insufficient for granting the requested indication in section 4.1 of the SmPC. The effectiveness of Ethinylestradiol/Drospirenon 24+4 Berlipharm for PMDD when used for more than three menstrual cycles has not been evaluated. Replication of the study results of the parallel study A21566 is necessary before the indication can be approved for section 4.1 of the SmPC.

However, the RMS considered the data obtained in the pivotal clinical trial in the treatment of PMDD are in line with the qualifications for inclusion in section 5.1 as described in the EC Guideline on the SmPC (2005) for inclusion of clinical data other than supporting the indication in section 4.1.

Efficacy

The clinical development program for PMDD is based on two phase III studies. The parallel study is considered the pivotal trial.

- The amount of clinical evidence in support of the treatment of emotional and physical symptoms of PMDD is considered insufficient for inclusion in SmPC section 4.1. Replication of the efficacy results of the 3-month parallel study A21566 is necessary before the indication can be approved for section 4.1 of the SmPC.
  This conclusion is based on the following considerations:
  - In response to the 'Potential Serious Risk to Public Health' raised by the RMS in the first round regarding the lack of efficacy data beyond 3 treatment cycles, the MAH has explained that the daily charting of the extensive DRSP questionnaire is burdensome for the women in a PMDD study of 6 treatment cycles. In addition, reference is made to the public literature, in which 29 different randomised controlled trials of SSRIs versus placebo had 3 or less treatment cycles, except for one study. [18] This study of Steiner et al. 2005 was the only study with a longer study length of 6 months: 2 run-in cycles followed by 6 treatment cycles. Although a different approach was used by asking women to daily report the severity for only 3 symptoms using visual analogue scales in contrast to the DRSP Questionnaire (21 items), the drop-out rate was high, i.e. 42.5%, in this study. Due to the daily charting of more than 20 questions and the long total study duration of 8 months (2 run-in cycles + 6 treatment cycles), the MAH expected a high drop-out rate in the requested parallel study with a study duration of 6 treatment cycles.

    The RMS concurred with the MAH that with such a thorough study design comprising the DRSP questionnaire, it is expected that the drop-out rate may be high. The drop-out rate of the parallel study was 28%. It was expected that the drop-out rate of a parallel study of 6 treatment cycles with the same study design as A21566 would be even higher, thereby impairing the validity of the results.

    The RMS acknowledged the reasoning that asking for a study of 6 treatment cycles with a similar design as the pivotal study is not feasible. However, as the type II variation was a request for a new indication and the clinical documentation is primarily based on one parallel study A21566, the

[18] Brown J, O'Brien PM, Marjoribanks J, Wyatt K. Selective serotonin reuptake inhibitors for premenstrual syndrome. Cochrane Database Syst Rev 2009;2:CD001396.

amount of efficacy data for inclusion of the proposed indication in section 4.1 was still considered too limited. Replication of the study results of the parallel study A21566 was necessary before the indication could be approved for section 4.1 of the SmPC. The efficacy data of the first treatment period of the cross-over study could not be used for that purpose, as the number of participants is too limited (34 on Ethinylestradiol/Drospirenon 24+4 vs. 30 on placebo).
Therefore, the RMS phrased its final 'Potential Serious Risk to Public Health' as:
"The amount of clinical evidence in support of the treatment of emotional and physical symptoms of PMDD is considered insufficient for inclusion in section 4.1. Replication of the efficacy results of the parallel study A21566 is necessary before the indication can be approved for section 4.1 of the SmPC".

- The RMS maintained its opinion that the efficacy data in the treatment of PMDD is in line with the qualifications for inclusion in section 5.1 as described in the EC Guideline on the SmPC (2005) for inclusion of clinical data other than supporting the indication in section 4.1.
"*If information from subgroup or post hoc analyses that is considered clinically relevant is presented and identified as such, this should be in a balanced way, which reflects the limited robustness of both positive and negative secondary observations. The magnitude of effects should be described using relative and absolute figures."*
This conclusion is based on the following considerations:
  - The primary endpoint based on the Full Analysis Set (FAS) population, i.e. the difference between treatment (baseline 77.4, reduction -37.5) and placebo (baseline 78.1, reduction -30.0) on the DRSP score the last 5 days before menses, was statistically significantly lower for Ethinylestradiol/Drospirenon 24+4, -7.5 (95% CIs -11.2, -3.80). This difference of 7.5 points corresponds to a 10% reduction to the common baseline score.
    This difference for Ethinylestradiol/Drospirenon 24+4 compared to placebo is modest but considered clinically meaningful. Other trials studying SSRIs in the treatment of PMDD with the DRSP questionnaire show a comparable treatment effect, i.e. 6.2% till 18.8%. Even more, the difference is similar to what has been observed for Fluoxetine 20 mg daily (9.0%) in Cohen et al. 2002. This study has been incorporated in section 5.1 of the harmonised fluoxetine SmPC, together with a second clinical trial:

    Two placebo-controlled studies were conducted in patients meeting Pre-Menstrual Dysphoric Disorder (PMDD) diagnostic criteria according to DSM-IV. Patients were included if they had symptoms of sufficient severity to impair social and occupational function and relationships with others. Patients using oral contraceptives were excluded. In the first study of continuous 20 mg daily dosing for 6 cycles, improvement was observed in the primary efficacy parameter (irritability, anxiety and dysphoria). In the second study, with intermittent luteal phase dosing (20 mg daily for 14 days) for 3 cycles, improvement was observed in the primary efficacy parameter (Daily Record of Severity of Problems score). However, definitive conclusions on efficacy and duration of treatment cannot be drawn from these studies.

  - The responder rates (defined as the percentage of subjects with at least a 50% reduction on the DRSP score from baseline) were significantly greater with Ethinylestradiol/Drospirenon 24+4 (48.4%) than placebo (36.1%) in the parallel study. This 12.3% difference between Ethinylestradiol/Drospirenon 24+4 and placebo is considered modest but clinically relevant by the RMS.

  - The MAH provided additional statistical analyses that used even a more conservative approach but nevertheless the results remained in support of the clinical efficacy of the parallel study A21566.

  - On basis of the additional analyses on the primary endpoint of the cross-over study A07545, it can be concluded that the results of the first treatment period of this small study are supportive of the primary efficacy endpoint in the pivotal study (A21566). The crossover-study randomized only 34 subjects to Ethinylestradiol/Drospirenon 24+4 Berlipharm and 30 subjects to Placebo. Only for 26 subjects in the Ethinylestradiol/Drospirenon 24+4 group and 23 subjects in the Placebo group a

baseline was established in the first treatment period. Consequently, the cross-over study is not considered a major trial, and inclusion of the cross-over study in 5.1 is not acceptable.

The RMS proposed the following text for inclusion in section 5.1 of the SmPC:

One ~~Two~~ multicenter, double-blind, randomized, placebo-controlled ~~studies were~~ study was performed to evaluate the efficacy and safety of Ethinylestradiol/Drospirenon 24+4 in women meeting premenstrual dysphoric disorder (PMDD) diagnostic criteria according to DSM-IV. The ~~first~~ study, using a parallel group design, was conducted in 449 reproductive-aged women with PMDD, confirmed by prospective daily ratings of their symptoms. Subjects were randomly assigned to receive Ethinylestradiol/Drospirenon 24+4 or placebo treatment for 3 cycles. ~~In the second study, using a crossover design, 64 women of reproductive age were treated with Ethinylestradiol/Drospirenon 24+4 or placebo for 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.~~

*Efficacy was assessed based on the change from baseline of the total score of the first 21 items of the Daily Record of Severity of Problems (DRSP) scale. After three months of treatment, in comparison with placebo, Ethinylestradiol/Drospirenon 24+4 showed a statistically significantly greater reduction of 10**.0**% for the percent change (48.4% versus 38.4%) in DRSP scores ~~in the parallel study~~. In addition, a higher percentage of subjects i.e. 12.3% (48.4% versus 36.1%), showed a fifty percent reduction in their DRSP scores. ~~The cross-over study supported these results~~. The effectiveness of Ethinylestradiol/Drospirenon 24+4 for PMDD when used for more than three menstrual cycles has not been evaluated.*

Safety

Adverse event pattern

- The overall percentage of related AEs was higher in Ethinylestradiol/Drospirenon 24+4-treated women in the PMDD studies (61.1% with at least one related AE) as compared to Ethinylestradiol/Drospirenon 24+4-treated women in the oral contraception (OC, 30.4%) and acne (27.8%) studies. Likewise, more AEs were reported in the placebo group in the PMDD studies as compared to placebo group in the acne studies. Thus, most likely, the study population in the PMDD studies had PMDD-symptoms, which were recorded as adverse events.

- The following treatment-emergent AEs, indicated by one member state, were higher in the Ethinylestradiol/Drospirenon 24+4- versus the placebo-group: Asthenia (19/231 (8.23%) vs. 8/218 (3.67%)), libido decreased (11/231 (4.76%) vs. 3/218 (1.38%)), emotional lability (10/231 (4.33%) vs. 3/218 (1.38%)), depression (8/231 (3.46%) vs. 2/218 (0.92%)) and nervousness (5/231 (2.16%) vs. 2/218 (0.92%)).
  These AEs were already listed in the table in the SmPC of Ethinylestradiol/Drospirenon 24+4, as common (emotional lability) or uncommon (depression, libido decreased, nervousness, asthenia). The data do not give rise to any additional safety concerns as compared to the findings documented for the OC studies. The ADRs reported in the PMDD studies were either expected for women suffering from PMDD or are well-known side-effects of OCs.

- The RMS was of the opinion that the adverse event profile is more favourable for COCs, including Ethinylestradiol/Drospirenon 24+4, than noted for SSRIs that are currently recommended as first choice in the treatment of PMDD in gynaecological guidelines. Main adverse events described are e.g. drowsiness, nausea, dizziness, constipation, sleep abnormalities, convulsions, hallucinations, and cardiovascular effects (increase in blood pressure, heart rate, and cholesterol levels). Furthermore, when treatment is discontinued, a withdrawal syndrome often occurs especially when discontinuation is abrupt, which includes flushes, dizziness, paraesthesia, headache, anxiety and nausea. Additionally it is noted that especially in adolescents there is a risk of suicidal behaviour.

Adverse events that led to discontinuation

- The percentage of Ethinylestradiol/Drospirenon 24+4-treated women (14.0%) who discontinued study treatment due to AEs was higher as compared to the OC (6.8%) and acne (5.6%) studies. The ADRs reported in the PMDD studies were either expected for women suffering from PMDD or are well-known side-effects of OCs.

  The most common reasons for discontinuation, as indicated by the MAH, were nausea (11 women (4.8%) in Ethinylestradiol/Drospirenon 24+4-group and 2 women (0.7%) in Placebo-group) and intermenstrual bleeding (8 women (3.5%) in Ethinylestradiol/Drospirenon 24+4-group and 0 women in Placebo-group). Both events are classified as "common" in the Ethinylestradiol/Drospirenon 24+4 SmPC. The RMS agrees with the MAH that intermenstrual bleeding usually subsides during continued treatment, and that it is possible that woman suffering from PMDD and choosing Ethinylestradiol/Drospirenon 24+4 as her method of contraception is more willing to accept the well-known temporary undesirable effects of hormonal contraception. The data did not give rise to any additional safety concerns as compared to the findings documented for the OC studies.

Serious adverse events

- Five serious adverse events were reported. None of the SAEs considered treatment-related gave rise to new safety concerns as compared to the risks already known for low-dose combined OCs.

Balance

A modest but clinically relevant effect was observed in the parallel study for Ethinylestradiol/Drospirenon 24+4 Berlipharm compared to placebo over 3 months of treatment. The size of the observed effect was similar to that observed for Fluoxetine 20 mg in the study of Cohen et al. 2002. This study is one of the two trials incorporated in 5.1 of the harmonised fluoxetine EU SmPC. The adverse event profile is more favourable for COCs, including Ethinylestradiol/Drospirenon 24+4, than noted for SSRIs that are currently recommended as first choice in the treatment of PMDD in gynaecological guidelines. Main adverse events are SSRI-like symptoms (dry mouth, insomnia, dizziness, headache, gastro-intestinal disturbance), cardiovascular adverse events (increase in blood pressure and heart rate) and withdrawal symptoms after discontinuation. For Ethinylestradiol/Drospirenon 24+4, no additional safety concerns were identified as compared to those documented for the oral contraception studies.
The RMS concluded the following: Though the safety profile of Ethinylestradiol/Drospirenon 24+4 Berlipharm is more favourable than noted for SSRIs, the efficacy data are currently too limited to grant an indication, as there is only one parallel study with modest efficacy in the submitted dossier. A second study is required with the same study design as applied in the placebo-controlled parallel study A21566. Nonetheless, the data fulfill the requirements for inclusion in section 5.1.

Discussion in Board meetings

The proposed PMDD indication was discussed in several Board meetings. On 4 June 2009 the Medicines Evaluation Board of the Netherlands came to its final conclusion that addition of the indication to section 4.1 of the SmPC is not approvable based on the data provided. Inclusion of the clinical data in section 5.1 was considered justified.

IV.2 CHMP referral and subsequent withdrawal

At the end of the variation application no agreement was reached between member states.
The concerned member states supported the RMS' decision to not grant an indication. However, member states disagreed on mentioning the study results on PMDD of phase III study A21566 in section 5.1 of the SmPC.
Therefore the procedure was referred for arbitration under Article 6 (12) of Regulation (EC) No 1084/2003 to the CHMP in July 2009, based on the following 'Potential Serious Risks to Public Health' raised by concerned member states:

1. The efficacy and safety of Ethinylestradiol/Drospirenon 24+4 Berlipharm for the treatment of PMDD has not been demonstrated.

2. The therapeutic indication PMDD is not approvable due to the lack of robust clinical evidence, therefore, the data should not be included in 5.1. The Guideline on SmPC states that only information relevant to the prescriber may be presented. Information about non-approved indications under 5.1 could easily be misinterpreted and encourages practitioners for off-label use.
3. In the pivotal study, less than 30% of patients who were considered eligible for the therapy by investigator met the strict inclusion criteria and were randomised. Only very carefully selected patients may benefit of the therapy, however, in clinical practice 2-month daily symptom recording before starting the therapy is very difficult to achieve. Since it may be difficult to identify suitable patients in clinical practice, there is a huge potential for misuse. Drop-out due to the treatment-related adverse events was much higher for the active arm compared to the placebo arm, and during the 3-month treatment 30% of patients were lost. These data supports negative benefit-risk balance.
4. It is not agreed with the MAH that longer than 3 month placebo controlled study is not feasible. PMDD is a chronic condition and long-term treatment will be used in clinical practice. Robust clinical evidence (at least 6 month placebo controlled data) is needed, especially since large placebo effect is expected. The MAH argues that high drop-out is expected due to the requirement to fill a questionnaire. However it should be noted that the drop-out was higher for the active treatment phase.
5. The total number of patients treated with Ethinylestradiol/Drospirenon 24+4 Berlipharm for PMDD is too small and more than one confirmative study is needed.

The CHMP initiated the referral procedure in July 2009. However, the CHMP was formally notified by the MAH of its decision to withdraw its MRP variation application from the member states on 10 February 2010.

V CHANGES IN PRODUCT INFORMATION

Not applicable.

ANNEX II – Submitted variation for addition of indication *Treatment of moderate acne vulgaris only in women seeking oral contraception* (NL/H/1270/001/II/006)

I RECOMMENDATION

Based on the review of the data on safety and efficacy, the type II variation for Ethinylestradiol/ Drospirenon 24+4 Berlipharm for addition of the indication *Oral contraception for women with moderate acne vulgaris. This treatment does not exempt patients from specific acne treatment if necessary*, is not approvable.

As there was no consensus reached within the CMD(h) between member states during the initial variation procedure, this final decision was reached through a CHMP referral.

The Committee reviewed the two main studies presented by the company to support the new indication and noted the overall effectiveness of Ethinylestradiol/Drospirenon 24+4 compared with placebo in the treatment of acne.
The Committee also considered the known risks with Ethinylestradiol/Drospirenon 24+4, including venous thromboembolism (VTE). Since acne is a common problem in young women, the CHMP was concerned that the risk minimisation measures proposed by the company to ensure that this medicine would be used to treat acne only in women seeking oral contraception were not sufficient. Women not seeking contraception would therefore be unnecessarily exposed to the risks of Ethinylestradiol/Drospirenon 24+4 Berlipharm when alternative acne treatments are available. The European Commission issued its refusal decision on 6 July 2012.

II EXECUTIVE SUMMARY

II.1 Introduction and scope of the variation

Ethinylestradiol/Drospirenon is indicated for oral contraception. Ethinylestradiol/Drospirenon 24+4 Berlipharm has been approved in all member states in Europe, except Hungary and Liechtenstein, following an MRP (NL/H/1270/001) with the Netherlands as RMS.

This annex concerns variation procedure NL/H/1270/001/II/006 regarding an additional indication *Treatment of moderate acne vulgaris only in women seeking oral contraception*. The same dosage regimen is applied as for the oral contraception indication. During the procedure, based on member states' comments, the proposed wording of the indication was *Oral contraception for women with moderate acne vulgaris only in women for whom hormonal contraception with ethinylestradiol/ drospirenone is indicated. This treatment does not exempt patients from specific acne treatment if necessary.*

The clinical documentation in support of this type II variation consisted of 2 double-blind placebo-controlled trials [A25152 (EE/DRSP: 229, Placebo: 227 subjects) and A25083 (EE/DRSP: 222, Placebo: 215 subjects)].
Currently, as established during the MRP, the results of these two placebo-controlled studies, which evaluated efficacy-safety of Ethinylestradiol/Drospirenon 24+4 in the treatment of acne are included in section 5.1 of the SmPC.

The acne indication was also part of the MRP registration procedure, which ended in a CMD(h) referral. The MAH then decided during the MRP registration procedure to pursue only the application for the indication of oral contraception.

III SCIENTIFIC DISCUSSION

III.1 Quality aspects

Not applicable.

III.2 Non-clinical aspects

Environmental risk assessment
The acne indication was part of the initial application for mutual recognition and therefore included in the initial Environmental Risk Assessment (ERA). Hence, an assessment in the context of this variation application was not deemed necessary.

III.3 Clinical aspects

III.3.1 Clinical pharmacology

Pharmacodynamics
Hormone levels
The change from baseline to cycle 6 was measured for total testosterone, free testosterone, DHEA-S, sex-hormone-binding globuline (SHBG), and androstenedione in a subpopulation of subjects in one of the two acne studies (A25083) (18 subjects in the DRSP/EE group and 18 subjects in the placebo group). There was a statistically significant decrease in the mean change from baseline to endpoint in free testosterone in the DRSP/EE group compared with the placebo group (p=0.0024). There was a statistically significant increase in the mean change from baseline to endpoint in SHBG in the DRSP/EE group compared with the placebo group (p=0.0022). These hormonal changes are what would be expected from low dose oral contraceptives. None of the other hormones evaluated showed any statistically significant differences between treatment groups.

III.3.2 Clinical efficacy

Clinical efficacy of Ethinylestradiol/Drospirenon in the treatment of moderate acne vulgaris is based on the data of 2 pivotal clinical placebo-controlled 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 approximately 40 women in study A25083.
A summary of design, number of participants, treatments and end points is presented in the table below:

Table 1: Overview of clinical phase III studies to demonstrate the efficacy of Ethinylestradiol/ Drospirenon 24+4 in the treatment of moderate acne vulgaris

Study	Short 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)

A25152 **US**	moderate acne vulgaris multicenter, double-blind, randomized, placebo-controlled	EE/DRSP: 222 Placebo: 215	6 cycles	or '1' (almost clear skin) on the 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.

T* Note: the number of women refers to the amended FAS (subjects with a minimum of 40 lesions, *i.e.* at least 20 inflammatory lesions and at least 20 non-inflammatory lesions), The amended FAS analysis concerned 'moderate acne vulgaris' rather than 'mild or moderate acne vulgaris'.

Justification of the placebo-controlled design

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[2], Lucky et al. 1997[3]). 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.

Justification of the primary endpoints selected

The definition of the standards for evaluation of clinical response to acne treatment were addressed in methodological reviews (Lehmann et al. 2002[19], Del Rosso, 2006[20]).

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

[19] Lehmann HP, Robinson KA, Andrews JS, Holloway V, Goodman SN. Acne therapy: a methodologic review. J Am Acad Dermatol. 2002 Aug;47(2):231-40.
[20] Del Rosso JQ. Defining criteria used to evaluate response to treatment of acne vulgaris. Cutis. 2006 Aug;78(2):117-21.

lesion count, investigators' static assessment as well as a self-assessment rating by the patients, addressed both objective and subjective endpoints.

Inclusion- and exclusion criteria
In both studies A25083 and A25152, similar inclusion and exclusion criteria were utilized:

Inclusion criteria

- women in good general health, between 14 and 45 years old, ≥ 1 year post-menarche, requesting treatment for moderate acne vulgaris,
- no contraindications for OC use
- Smokers were to be recruited only up to a maximum age of 30 years.
- 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 ISGA scale[21].

- 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 (e.g. Norplant®) or hormonal contraceptive intrauterine devices/systems (e.g. Mirena®)
  - two months free of oral contraceptives
  - six months free of systemic isotretinoin (e.g. Accutane®) or injectable contraception (e.g. Depo-Provera®)
  - 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)

Methodology
The methods of dermatological assessment, the study design and the efficacy variables were similar in both clinical studies. As no relevant differences could be observed between the individual study results and the pooled analysis, results of the pooled analysis are summarized and discussed below.

Primary efficacy variables

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

The endpoint for efficacy analysis was visit 5 (day 17 – 24 of cycle 6), with missing values replaced by the last observed value carried forward.

Table 2 summarizes the methods applied to evaluate the primary efficacy variables of studies A25083 and A25152 relevant to the use of Ethinylestradiol/Drospirenon 24+4 Berlipharm 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

[21] ISGA is 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 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; 3 = lesions predominate, with multiple inflammatory lesions evident: Several to many comedones and papules/pustules, and there may or may not be one small nodulocystic lesion; 4 = inflammatory lesions are more apparent: many comedones and papules/pustules, there may or may not be a few nodulocystic lesions; 5 = highly inflammatory lesions predominate: variable number of comedones, many papules/ pustules and nodulocystic lesions.

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.
Percentage change in non-inflammatory lesions (open comedones and closed comedones)	
Percentage change in total lesions (inflammatory and non-inflammatory)	
Investigator Static Global Assessment (ISGA)	ISGA was obtained at screening and at each scheduled treatment visit[21].

Secondary efficacy variables

- Change from baseline in count of papules
- Change from baseline in count of pustules
- Change from baseline in count of nodules
- Change from baseline in count of open comedones
- Change from baseline in count of closed comedones
- 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)
- 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).

For all primary and secondary efficacy variables an FAS analysis and an amended FAS analysis were performed. The original inclusion criterion (10 to 100 comedones, 10 to 50 inflammatory lesions, and not more than 5 nodules) was amended in the early course of the studies upon request of the FDA in order to change the indication from 'mild to moderate acne vulgaris' to 'moderate acne vulgaris'. Therefore also the FAS was amended. Additionally, a PPS analysis was done for the primary efficacy variables. The amended FAS analysis was considered to be the 'primary' analysis. The endpoint for efficacy analysis was visit 5 (day 17 – 24 of cycle 6), with missing values replaced by the last observed value carried forward. Percentage change from baseline in lesion count at a given visit is defined as (lesion count at visit – lesion count at baseline)*(100/lesion count at baseline).

Sample size determination

Two published reports[22,23] compared the efficacy of a triphasic, combination oral contraceptive (norgestimate-ethinylestradiol) to placebo for treatment of moderate acne. For these studies, the averages of the mean percent difference from baseline in lesion counts (baseline – cycle 6) * (100/baseline) for the Intent-to-Treat groups were, for inflammatory lesions: 47.80 for treatment and 30.26 for placebo (with a pooled SD of 50.16) and for total lesions: 41.74 for treatment and 27.52 for placebo (with a pooled SD of 39.02). A sample size of 250, assuming a dropout rate of 20%, would provide greater than 90% power to detect differences of these magnitudes. Assuming a common SD of 55 (the pooled SD for non-inflammatory lesions observed in these studies) and a 20% dropout rate, 90% power would be provided to detect a difference between treatment and placebo of 18.0 percent in non-inflammatory lesions. Assuming that 40 percent of the subjects in the active treatment group are classified as "clear" or "almost clear" on the ISGA, and a 20% dropout rate, this sample size would provide a greater than 90 to detect a difference of 16 percent or greater between active treatment and placebo.

[22] Redmond GP, Olson WH, Lippman JS, Kafrissen ME, Jones TM, Jorizzo JL. Norgestimate and ethinyl estradiol in the treatment of acne vulgaris: A randomized, placebo-controlled trial. Obstetrics and Gynecology 1997;89:615-22.

[23] Lucky AW, Henderson TA, Olson WH, Robisch DM, Lebwohl M, Swinyer L. Effectiveness of norgestimate and ethinyl estradiol in treating moderate acne vulgaris. Journal of the American Academy of Dermatology 1997;37:746-54

A successful outcome for Ethinylestradiol/Drospirenon in the treatment of moderate acne vulgaris was defined as:

- Statistically significantly greater reductions in the percentage change from baseline to treatment endpoint (day 17 – 24 of cycle 6) 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 (cycle 6) (FDA response to Special Protocol Assessment; 12 Dec 2002).

Results

- Disposition

Overall, a total of 893 women were assigned to the amended FAS of the efficacy assessment, 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. As recommended by the FDA, all randomized women who were dispensed study medication were included in the analysis regardless of having any post-baseline data.

- Demographics

An analysis of demographic and baseline characteristics (including dermatological baseline findings, gynecological, 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 2 treatment groups. Concomitant medications were taken by slightly more than half of the women in both treatment groups (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 (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%).

Baseline findings of lesion counts

An analysis of demographic and baseline characteristics (including dermatological baseline findings, gynecological, 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. The baseline findings of lesion counts are summarized in table 3.

Table 3: Baseline findings of lesion counts and ISGA scale by study and treatment group – amended FAS

Parameters mean count ± SD	Study A25083 EE/DRSP: N=229 Placebo: N=227	Study A25152 EE/DRSP: N=222 [1] Placebo: N=215	Pooled data EE/DRSP: N=451 [1] Placebo: N=442
Inflammatory lesion count			
total	EE/DRSP: 32.6 ± 16.1 Placebo: 33.1 ± 14.6	EE/DRSP: 31.7 ± 12.3 Placebo: 31.8 ± 13.6	EE/DRSP: 32.1 ± 14.4 Placebo: 32.4 ± 14.2
papules	EE/DRSP: 22.4 ± 11.0 Placebo: 22.9 ± 11.5	EE/DRSP: 23.2 ± 11.2 Placebo: 22.9 ± 12.1	EE/DRSP: 2.8 ± 11.1 Placebo: 22.9 ± 11.8
pustules	EE/DRSP: 9.6 ± 10.4 Placebo: 9.6 ± 10.4	EE/DRSP: 8.0 ± 6.8 Placebo: 8.5 ± 7.2	EE/DRSP: 8.9 ± 8.8 Placebo: 9.1 ± 9.0
nodules	EE/DRSP: 0.6 ± 1.0 Placebo: 0.5 ± 1.0	EE/DRSP: 0.4 ± 0.8 Placebo: 0.4 ± 0.8	EE/DRSP: 0.5 ± 0.9 Placebo: 0.5 ± 0.9
Non-inflammatory lesion count			
total	EE/DRSP: 47.1 ± 31.4 Placebo: 47.0 ± 30.8	EE/DRSP: 43.9 ± 22.8 Placebo: 43.8 ± 25.8	EE/DRSP: 45.5 ± 27.5 Placebo: 45.4 ± 28.5
open comedones	EE/DRSP: 19.4 ± 19.3 Placebo: 20.6 ± 24.5	EE/DRSP: 21.8 ± 25.2 Placebo: 22.1 ± 25.5	EE/DRSP: 20.6 ± 22.4 Placebo: 21.4 ± 25.0
closed comedones	EE/DRSP: 27.7 ± 22.2 Placebo: 26.3 ± 20.3	EE/DRSP: 22.1 ± 15.2 Placebo: 21.7 ± 15.4	EE/DRSP: 24.9 ± 19.2 Placebo: 24.1 ± 18.2
Total lesion count	EE/DRSP: 79.6 ± 42.3 Placebo: 80.0 ± 37.4	EE/DRSP: 75.6 ± 30.5 Placebo: 75.6 ± 33.7	EE/DRSP: 77.6 ± 37.0 Placebo: 77.9 ± 35.7
ISGA scale (number of women per rating)	EE/DRSP: 2: 2 3: 132 4: 81 5: 14 Placebo: 2: 2 3: 126 4: 91 5: 8	EE/DRSP: 2: 4 3: 130 4: 73 5: 14 Placebo: 2: 2 3: 123 4: 76 5: 14	EE/DRSP: 2: 6 3: 262 4: 154 5: 28 Placebo: 2: 4 3: 249 4: 167 5: 22

[1] In the EE/DRSP group, for 221 out of 222 women baseline values were available in study A25152.

Primary Efficacy Variable Results

- Inflammatory lesions

Comparison between treatment groups of mean percentage 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, Table 4). Endpoint was defined as visit 5 (i.e. days 17 to 24 of cycle 6), with missing values replaced by LOCF.

- 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 the post-baseline visits in cycle 3 and 6, but not in cycle 1.

- 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 percentage 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).

- 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. 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).

- Summary of primary endpoint results

Table 4 gives an overview of the results of the primary efficacy endpoint:

Table 4: Overview of primary efficacy variable results - amended FAS (pooled data of studies A25083 and A25152)

Amended FAS **EE/DRSP: N= 451** **Placebo: N=442**	**Percentage 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 versus 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 centre 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 as well as within placebo groups. However, the reductions in all the counts were markedly 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.

- Summary of secondary efficacy results

Statistically significantly greater 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.

- Results of additional analyses

Hirsutism scale score
Most of the subjects in both treatment groups did not have any change in hirsutism scale score for the upper lip and chin by endpoint (day 17 – 24 of cycle 6).

- Comparison of results in subpopulations

As recommended by the FDA, the MAH performed subgroup analyses of the primary efficacy variables 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.

Conclusion on efficacy

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 endpoints chosen to evaluate efficacy of Ethinylestradiol/Drospirenon 24+4 Berlipharm in the treatment of moderate to severe acne vulgaris is considered adequate. Apart from the improvement of 2 of the 3 lesion counts, the primary endpoint 'clear or almost clear' rating is considered a good addition to lesion count as it represents a very relevant clinical outcome from a patient's point of view. Combining these endpoints contributes to the overall picture of the efficacy of the preparation.

A significantly greater improvement versus placebo-treatment was noted both in lesion counts and in investigator 'clear' or 'almost clear' rating. The reduction in lesion counts achieved is comparable with that reported with other COC treatments and with different topical treatments (retinoids), including topical antibiotics, published in literature. A 'clear' to 'almost clear face' was achieved in up to 23% of patients after 6 months of treatment, which is lower than considered in the sample size considerations (40%), but the difference with placebo is nevertheless considered clinically relevant. Additionally, maximum improvement may not yet be reached at 6 months treatment for a chronic condition like acne, which is supported by the outcome as no plateau in efficacy endpoint was yet reached. This extra efficacy endpoint is not commonly used in published COC studies in acne treatment, so it is unclear whether this outcome is in line with other treatments.

In conclusion, the efficacy of Ethinylestradiol/Drospirenon Berlipharm in the treatment of moderate to severe acne is considered adequately proven.

III.3.3 Clinical safety

Only the safety profile in both acne studies is presented. For overall safety results in both the indications OC and acne, refer to page 14-15 of this report (initial MRP assessment).

- Safety population

The mean age of women included in the 2 studies was approx. 25 years in both the Ethinylestradiol/ Drospirenon Berlipharm and placebo groups. An analysis of demographic parameters by study revealed that the study populations included in the individual studies and treatment groups were mostly comparable with respect to their demographic parameters. The demographic characteristics of the overall safety population can be considered representative of the EE/DRSP target population.

- Adverse events

In comparison to the clinical studies to investigate Ethinylestradiol/Drospirenon Berlipharm as an OC, the overall rate of ADRs for EE/DRSP-treated women was similar in the clinical studies to investigate EE/DRSP in the treatment of moderate acne vulgaris: in the acne studies 27.8% of the EE/DRSP-treated population experienced ADRs compared to 30.4% (24.5% if abnormal laboratory values classified as AEs based on a predefined algorithm were excluded) in the OC studies. As a result of the differences in AE recording, ADRs related to menstrual disorders were considerably higher in the EE/DRSP-treated acne population.

A comparison of Ethinylestradiol/Drospirenon Berlipharm with placebo revealed that metrorrhagia, headache, nausea and emotional lability were common AEs in both treatment groups. AEs that were only common among the EE/DRSP-treated women were menorrhagia, breast pain, dysmenorrhea, menstrual disorder, depression and vomiting; these were uncommon in the placebo group. Migraine was a common AE in the placebo group but classified as uncommon in the EE/DRSP group. None of the SAEs recorded in the course of the acne studies was considered to be related to the study medication.

The percentage of women with AEs leading to study discontinuation (4.8%) was considered low and similar in the EE/DRSP and placebo groups.

Events of cancer considered medically relevant with respect to the safety of the investigational product were not observed. There were no thromboembolic events reported in the course of studies A25083 and A25152 evaluating Ethinylestradiol/Drospirenon Berlipharm in the treatment of moderate acne vulgaris. None of the cardiovascular events were classified as serious or gave rise to new safety concerns as compared to the risks already known for low-dose combined OCs.

- Post-marketing experience

Based on the Periodic Safety Update Reports, which include a safety assessment of the products Yasmin, Yasminelle and Yaz (Ethinylestradiol/Drospirenon 24+4), and based on an ongoing safety surveillance of these products a favorable risk-benefit ratio is confirmed. The reports of the International Active Surveillance Study of Women taking Yaz (INAS Yaz) a large observational study comparing a cohort of mainly Yaz (Ethinylestradiol/Drospirenon 24+4), but also Yasmin users with a cohort of other OC users with regard to rare serious adverse outcomes as part of the risk management program for Ethinylestradiol/Drospirenon Berlipharm, did not suggest a risk difference versus other COCs.

- Risk management plan

A Risk Management Plan for Ethinylestradiol/Drospirenon 24+4 Berlipharm has been assessed during the application for marketing authorisation. The RMP was considered acceptable. As part of this type II variation, assessment of the RMP is focused on the appropriateness for the proposed indication "Treatment of moderate acne vulgaris only in women seeking oral contraception".
Although the proposed indication is the treatment of moderate acne vulgaris in women seeking oral contraception, off-label use in women with acne vulgaris who are not seeking oral contraception is conceivable.
In the addendum to the RMP, risk minimisation activities were proposed for this issue:

- An education outreach program to reduce potential off label use with launch of Ethinylestradiol/ Drospirenon 24+4 Berlipharm.
- Two independently conducted drug utilization studies:
  - New drug utilization study to monitor:
    - EE/DRSP prescribing practices in Europe and
    - the effectiveness of the educational outreach program
  - Adaptation of the INAS study to monitor:
    - EE/DRSP off label prescribing practices in Europe and
    - a potential public health risk due to EE/DRSP off label use.

Conclusion on safety
The pattern of adverse drug reactions (ADRs) observed in both acne studies does not indicate any additional safety issue than seen in the contraception studies performed with Ethinylestradiol/Drospirenon 24+4. Post-marketing surveillance is covered by INAS Yaz. For off-label use in women with acne vulgaris who are not seeking oral contraception, risk minimization activities have been laid down.

IV UPDATED DISCUSSION, OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

IV.1 Benefit-risk assessment of the RMS

Benefit
The clinical evidence in support of treatment of moderate acne only in women seeking oral contraception is relevant and robust, which conclusion is based on the following considerations:

- A clinically relevant effect on acne versus placebo has been shown;
- The placebo-controlled trials are designed according to the strictest 'state of the art' regulatory recommendations for placebo-controlled trials.

- The absence of active-controlled studies is considered acceptable as no 'gold standard' can be identified as alternative treatment option within the class of COCs, and no suitable comparator drug was available for clinical trials.

Risks

- The safety profile observed in both acne studies is comparable with that shown in the contraception studies performed with Ethinylestradiol/Drospirenon 24+4 Berlipharm.
- The target population for the acne indication has been limited to a group that is prescribed an oral contraceptive. However, to address the concern that there might be an "off-label" use of EE/DRSP, *i.e*. use as an acne treatment for women who do not seek oral contraception, the MAH is prepared to initiate a risk minimization program, consisting of an education outreach program to reduce potential off-label use with launch of Ethinylestradiol/Drospirenon 24+4 Berlipharm and two independently conducted drug utilization studies to assess potential 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 utilization study, the MAH would also commit to work with local health authorities and professional prescribing organizations to improve and 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, prolonged antibiotic therapy carries a risk of inducing resistance and could reduce efficacy of hormonal contraception.

Discussion in Board meetings

The proposed acne indication was discussed in several Board meetings. During the national procedure in 2006, and during the mutual recognition procedure in 2008, the Board concluded that the benefit/risk ratio of Ethinylestradiol/Drospirenon 24+4 0.02 mg/3 mg Berlipharm in 'treatment of moderate acne vulgaris only in women seeking oral contraception' is favourable. In the subsequent variation procedure the Board came to the same conclusion.

Member states' discussion on benefit/risk

During the variation procedure concerns were raised by a number of Concerned Member States. These were objections regarding the safety of use (risk of VTE), issues regarding the duration of the clinical trails (6 months), lack of comparative information regarding other acne treatments, and off-label use. Based on comments the revised wording of the proposed indication was *Oral contraception for women with moderate acne vulgaris only in women for whom hormonal contraception with ethinylestradiol/drospirenone is indicated. This treatment does not exempt patients from specific acne treatment if necessary.* This was however not accepted. Some member states had the opinion that an acne indication would encourage use of Ethinylestradiol/Drospirenon 24+4 over LNG-containing COCs with a better safety profile (lower VTE risk). Changing the wording of the indication would not address their concerns. Further, it was considered that the possibility of off-label use for the treatment of acne irrespective of the need of an oral contraceptive was likely to be high; monitoring of off-label use and start of Risk Minimisation activities would be inadequate.
Member states considered inclusion of the data on the 2 clinical studies in section 5.1 of the SmPC as sufficient.

Consensus between member states on whether acne could be included as an indication in section 4.1 of the SmPC could not be reached during the variation procedure.

IV.2 CHMP referral

On 28 June 2011, the Concerned Member States Italy and 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/Drospirenon 24+4 Berlipharm in the proposed indication was considered not acceptable in light of:

- the known greater risk of venous thromboembolic events (VTE) for DRSP-COCs in comparison with levonorgestrel (LNG)-COCs;
- the potential use of the product for women who are not comprised in the target population.

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 as the CHMP noted that other treatment options are available for the treatment of acne alone (e.g. topical antimicrobials). Therefore, the CHMP considered the 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.

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.

In the Board meetings of 12 October 2011 and 11 January 2012, during the CHMP referral, the Medicines Evaluation Board of the Netherlands maintained its positive position.

The Committee however, based on the above considerations, concluded that the variation application should be refused. The negative European Commission decision was issued on 3 July 2012.

For further details, refer to the following documents, available on the EMA website:

- ‘Questions and answers on Yaz 24+4 and Ethinylestradiol-Drospirenone 24+4 (ethinylestradiol/ drospirenone, 0.02 mg/3 mg tablets), EMA Doc. Ref. EMA/257547/2012 Rev.1,
- The ‘Referral assessment report’, EMA Doc. Ref EMA/399942/2012
- Annex II – ‘Scientific conclusions and grounds for refusal presented by the European Medicines Agency’
- The European Commission decision dated 6 July 2012, Doc. Ref. C(2012)4849.

These are available at:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Yaz/human_referral_000307.jsp&mid=WC0b01ac05805c516f

V CHANGES IN PRODUCT INFORMATION

Not applicable.