CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Yasminelle
Belanette
Liofora
Yasminelle 28
Belanette 28

Drospirenone and ethinylestradiol
Film-coated tablets, 3/0.02 mg

Schering Nederland BV, Weesp, The Netherlands

This assessment report is published by the MEB following 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.

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Pharmacotherapeutic group:	Progestogens and estrogens, fixed combinations
ATC code:	G03AA12
Route of administration:	oral use
Therapeutic indication:	oral contraception
Prescription status:	prescription only

Date of first authorisation (national):	*Yasminelle*	4 August 2005
	Belanette	21 November 2005
	Liofora	15 November 2005
	Yasminelle 28	17 November 2005
	Belanette 28	21 November 2005

Application type/legal basis: Directive 2001/83/EC, Article 8(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations see modules 2, 3 and 4.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the MEB has granted a marketing authorisation for Yasminelle, Belanette, Liofora, Yasminelle 28 and Belanette 28, film-coated tablets 3/0.02 mg from Schering Nederland BV. The first date of authorisation of Yasminelle was on 4 August 2005 in The Netherlands. The products are indicated for oral contraception.

A comprehensive description of the indications and posology is given in the SPC (see Module 3).

The marketing authorisation is granted based on article 8(3) of Directive 2001/83/EC.

Yasminelle contains 21 film-coated tablets 3/0.02 mg drospirenone (DRSP)/ethinylestradiol (EE). Belanette and Liofora are duplex applications of Yasminelle. When in this report Yasminelle is mentioned, this is also applicable for Belanette and Liofora.

Yasminelle 28 contains 21 film-coated tablet 3/0.02 mg drospirenone (DRSP)/ethinylestradiol (EE) (the same tablets as in Yasminelle) together with 7 film-coated tablets without active substances (placebo tablets). The assessment of Yasminelle applies also for Yasminelle 28. Belanette 28 is a duplex application for Yasminelle 28. When in this report Yasminelle 28 is mentioned, this is also applicable for Belanette 28.

One tablet Yasminelle is administered daily for 21 days followed by a 7-day tablet-free interval. For Yasminelle 28 the tablet free period is replaced by administration of placebo tablets.

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). Yasminelle is a low-dose formulation of Yasmin, in which the amount of EE is reduced from 0.03 mg to 0.02 mg.
The first marketing authorisation for Yasmin was granted in the Netherlands on 7 March 2000.
Additionally, Yasmin is approved on 8th of August 2000 in all EC countries at that time with The Netherlands as reference member state (Mutual Recognition Procedure NL/H/215, 217, 218/01).

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 the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance and excipients

The active substances are drospirenone and ethinylestradiol, both established active substances of which ethinylestradiol is described in the European Pharmacopoeia (Ph Eur). The active substance specifications are considered adequate to control the quality. The specification for ethinylestradiol meets the requirements of the monograph in the Ph. Eur. Batch analytical data demonstrating compliance with these specifications have been provided for 13 batches of drospirenone and for 9 batches of ethinylestradiol.

Full data on the synthesis and quality control have been provided for drospirenone.

The CEP procedure is used for ethinylestradiol. Under this 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, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Stability data on the active substances has been provided for 3 batches in accordance with applicable European guidelines demonstrating the stability of the active substance drospirenone for 5 years and demonstrating the stability of the active substance ethinylestradiol for 3 years

The excipients are described in the Ph Eur or USP. Ph Eur and USP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU and USA respectively.

Medicinal Product

Composition

The medicinal product is a film-coated tablet composed of 3 mg of the active substance drospirenone and 0.020 mg of the active substance ethinylestradiol. The active substance ethinylestradiol is present in the form of a clathrate (a molecular inclusion complex) with betadex (beta-cyclodextrin). The excipients are:

Tablets containing substances
Core: lactose monohydrate, maize starch, magnesium stearate
Coating: hypromellose, talc, titanium dioxide, ferric oxide.

Tablets not containing active substances (placebo tablets)
Core: lactose monohydrate, maize starch, povidone 25000, magnesium stearate
Coating: hypromellose, talc, titanium dioxide

The tablets are packed in PVC/Aluminium blister strips.

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.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product has been presented for 3 batches in accordance with the relevant European guidelines.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification is based on the monograph for tablets in the Ph Eur and includes tests for identification, assay, determination of the decomposition products, dissolution and content uniformity of both active substances and microbial contamination.
Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.
Satisfactory validation data for the analytical methods has been provided.
Batch analytical data from the proposed production sites have been provided, demonstrating compliance with the specification.

Stability tests on the finished product

Stability data on the product has been provided from 3 batches in accordance with applicable European guidelines. No specific storage conditions need to be included in the SPC or on the label. The stability data demonstrate that the product remains stable for 4 years.

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

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non clinical aspects

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 Yasminelle 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 SPC.

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

At the time of the authorisation of Yasmin, this subject was not yet assessed. For this reason, also no environmental risk assessment was made for Yasminelle. Yasminelle can be regarded as a substitute for Yasmin. It contains the same dose of drospirenone and two third of the dose of ethinylestradiol. Therefore the approval of Yasminelle will not result in an increase in the total quantity of drospirenone released into the environment. The total quantity of ethinylestradiol released into the environment will decline if Yasmin is substituted by Yasminelle. The product does not contain any component which results in additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Introduction

The product Yasminelle, is an orally administered preparation intended for oral contraception, containing. ethinylestradiol (EE) at a dose of 20 micrograms and the progestagen drospirenone (DRSP) at a dose of 3 mg.
DRSP is a rather new synthetic steroid hormone with progestagenic and slight aldosterone-antagonistic activity, intended for use as the progestagenic component of this oral combined contraceptive.
One tablet Yasminelle is administered daily for 21 days followed by a 7-day tablet-free interval. For Yasminelle 28 the tablet free period is replaced by administration of placebo tablets for 7 days.
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). Yasminelle is a low-dose formulation of Yasmin, in which the amount of EE is reduced from 0.03 mg to 0.02 mg. The MAH's rationale of the development program of Yasminelle is to provide a formulation of Yasmin with a lower EE dosage of 0.02 mg. 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 0.03 mg to 0.02 mg.
The contraceptive effect of Yasminelle 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 2 new pharmacodynamic ovulation inhibition studies; 7 new pharmacokinetic studies, and two clinical phase III studies. Additionally, cross-reference was done to the information in the registration dossier of Yasmin.

The specific guidance document "*Note for Guidance on Clinical Investigation of Steroid Contraceptives in Women*" (CPMP/EWP/519/98) was followed in the clinical studies.

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.

Clinical Pharmacology

Human pharmacokinetics

As the synthetic estrogen ethinylestradiol (EE) is well-known and has long been used in therapy and the clinical pharmacology of DRSP has been extensively studied during the development of Yasmin, the clinical pharmacokinetics studies performed for Yasminelle were primarily focused on relative bioavailability, single dose pharmacokinetics and multiple dose pharmacokinetics in healthy young women. In addition, drosperinone pharmacokinetics in women with impaired renal and liver function, and studies investigating drosperinone's drug interaction potential are summarised in this dossier, because these data were obtained after approval of Yasmin.

Drospirenone
After oral administration, drospirenone is rapidly and completely absorbed. The absolute bioavailability is about 85%. Concomitant ingestion of food has no influence on the bioavailability of drospirenone.
The different formulations used during the clinical studies did not differ clinically significant with respect to the rate and extent of absorption. The volume of distribution in steady state is about 4 L/kg and the total

clearance is estimated to be 1.5 mL/min/kg. Drospirenone is bound to plasma proteins for more than 95% and it does not bind to sex hormone binding globulin (SHBG)-related globulin's.

In steady state, the mean maximum concentration of drospirenone after administration of 3 mg is about 70 ng/mL ± 15%. The mean disposition half-life of drospirenone alone or in combination with ethinylestradiol is about 30h. Steady state is reached after 7 days in each cycle and after 5 cycles with an accumulation factor of 3. The pharmacokinetics of drospirenone can be described by a two compartment open model and is linear over the dosing range of 1 to 4 mg once daily.
Drospirenone is extensively metabolised after oral administration. At least 20 metabolites were identified. The two major metabolites, which do not show any pharmacological activity with respect to the steroid hormone receptor, are formed without involvement of the cytochrome P450 enzyme system.

The elimination half-life of the metabolites is approximately 57 hours. The pharmacokinetics of drospirenone is not influenced by co-administration of ethinylestradiol. Drospirenone is excreted by breast milk for about 0.6% of the daily oral dose.

Drospirenone did not show any inhibition of CYP3A4 or CYP2C19 in vivo.

Studies in patients with renal (mild to moderate) impairment and hepatic (moderate Child-Pugh class B) impairment indicate no clinically relevant change in pharmacokinetics of drospirenone. Clearance of drospirenone in moderate hepatic impaired patients decreases resulting in a subsequent twofold increase in exposure. However, the increased exposure was shown not to have a relevant impact on serum potassium levels in these patients.

Ethinylestradiol
The synthetic estrogen ethinylestradiol has long been used in therapy and the general pharmacokinetics of ethinylestradiol are considered to be sufficiently known.

Drospirenone and ethinylestradiol together
A limited impact of food on bioavailability was observed for both ethinylestradiol and drospirenone in the Yasmin dossier in a quarter of the subjects. This finding is not expected to lead to reduced contraceptive efficacy that is primarily driven by the progestagen compound. The same amount of progestagen, i.e. 3 mg drospirenone, is included in Yasminelle as in the higher dosed Yasmin and there is no restriction to food intake for that product. Bleeding control is driven by the estrogen component and may have an indirect effect on efficacy as increased breakthrough bleedings may lead to discontinuation. However, in an active controlled clinical trial versus Mercilon (ethinylestradiol 20 microgram + desogestrel 150 microgram), the bleeding pattern during Yasminelle use was similar to the pattern found during Mercilon use. Therefore, no restrictions to food intake are proposed.

The influence of concomitant administration of drospirenone on the pharmacokinetics of ethinylestradiol has been investigated in the Yasmin dossier. The pharmacokinetics of ethinylestradiol after multiple dosing of 30 microgram ethinylestradiol in combination with 2 and 4 mg drospirenone were similar in rate and extent of absorption with Microgynon® that also contains 30 microgram ethinylestradiol. It is therefore unlikely that drospirenone affects to a clinically significant extent the pharmacokinetics of ethinylestradiol. Relative bioavailability of ethinylestradiol is not influenced by the clathrate formation with betadex. The extent of absorption is similar and rate of absorption is comparable. A high fat meal did influence the bioavailability of ethinylestradiol significantly. A twofold accumulation of PK-parameters occurs in steady state conditions.

Human pharmacodynamics

The MAH has performed 2 new ovulation inhibition studies and 2 new studies on the risk of hyperkalaemia. Additionally, reference is made to the Yasmin dossier.

Inhibition of ovulation
The MAH has performed 2 new ovulation inhibition studies of which the design and choice of variables is in accordance with the CHMP Note for Guidance on investigation of steroid contraceptives.
The results obtained in these pharmacodynamic studies performed in Caucasian and Japanese women, have sufficiently demonstrated that treatment with Yasminelle results in an adequate degree of ovulatory inhibition.

Anti-mineralocorticoid properties
The MAH has performed 2 new studies on the risk of hyperkalaemia. Potassium levels are slightly increased in the subjects with mild to moderate renal impairment. In moderate (Child-Pugh class B) hepatic impairment no increase in serum potassium levels is observed, which is indicated by a ratio close to unity with a tight 90% confidence interval.
The applicant warns appropriately to be extra careful when administering drospirenone-containing products in its SPC and the clinical overview for patients with renal impairment, who use potassium sparing drugs or supplements. Women with acute renal failure or severe renal insufficiency are contra-indicated for use of Yasmin and Yasminelle.
As assessed in new studies with Yasminelle, the occurrence of hyperkalaemia based on an interaction with ACE-inhibitors or NSAID's, is considered unlikely.

Phase III confirmative study data

The main documentation in support of the efficacy includes 2 clinical phase III studies. In both studies the contraceptive efficacy, bleeding pattern and safety were investigated. The details are summarised in the next table.

Clinical studies for efficacy and safety

Study	Design	Number of patients	Treatment	Reference	N of cycles	Efficacy parameters
A15129 DE, CH 2000-2003	M,O,U,NC	516	3 mg DRSP/ 20 µg EE		26	Number of pregnancies (Pearl index), cycle control parameters and bleeding pattern, quality of life
A09653 BE,CZ, IT, UK 2001-2002	M,O,R,P,C	220 Yasminelle 221 Mercilon	3 mg DRSP/ 20 µg EE	Mercilon (20 µg EE/ 150 µg desogestrel)	7	cycle control parameters and bleeding pattern, pregnancies

BE=Belgium, CZ=Czech Republic, DE=Germany, IT=Italy, UK=United Kingdom
C= comparative, M= multicenter, NC= non-comparative, O= open, P= parallel, R= randomized, U= uncontrolled
DRSP=drosperinone, EE= ethinylestradiol

The following TT 4 summarises all efficacy variables of studies A09653 and A15129 relevant to the use of Yasminelle as oral contraceptive.

TT 4 Overview of efficacy parameters to support the indication

Pregnancies	PI calculation A human chorionic gonadotropin (HCG) urine test had to be performed by all volunteers before first tablet intake (on the first day of next menstrual bleeding) and if throughout the study no bleeding occurred until day 4 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.
Bleeding patterns	calculation of the number of - bleeding/spotting days - number of spotting only days - number of bleeding/spotting episodes - number of spotting only episodes Volunteers daily recorded bleeding intensity throughout the treatment phase using diary cards; the completed diary cards were collected at each visit. All evaluations derived from the daily bleeding record were to be performed at the responsible biometrics function.
Cycle control parameters	calculation/completion of - withdrawal bleeding (yes/no, length of withdrawal bleeding episode, maximum intensity of withdrawal bleeding episode, onset of withdrawal bleeding episode) - intracyclic bleeding (yes/no, number and maximum length of intracyclic bleeding episodes, number of intracyclic bleeding days, maximum intensity of intracyclic bleeding episodes) - women with intracyclic bleeding (number of volunteers with at least one intracyclic bleeding episode) Volunteers daily recorded bleeding intensity throughout the treatment phase using diary cards; the completed diary cards were collected at each visit. All evaluations derived from the daily bleeding record were to be performed at the responsible biometrics function.
Subjective assessment (quality of life)	At the final examination, the volunteer gave a subjective assessment of her well-being. The volunteer 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 wished to continue with the study medication.

PI=Pearl Index

In study A15129, pregnancy (present or not present) was investigated as primary efficacy variable; no such distinction between primary and secondary target variables was made in study A09653.

Study participants

The women in the studies had to fulfil the following criteria (inclusion criteria):

- Healthy, menstruating volunteer requesting contraception
- Age between 18 and 35 years (inclusive), smokers maximum age of 30 at inclusion
- Papanicolaou (Pap) smear taken or non-suspicious Pap smear within the last six months prior to start of the study could be presented
- At least three cycles had to follow delivery, abortion, or lactation before start of treatment
- At least six cycles had to follow depot contraception, at least one cycle had to follow desogestrel or drospirenone-containing oral contraceptives

Primary end points in contraceptive efficacy

- *Calculation of the Pearl Index*
  Contraceptive effectiveness was assessed by the Pearl Index (PI) for cycles in which no additional contraceptive method was used. Additionally, an adjusted PI corrected (PIc) was calculated taking intake failure into account.

  All volunteers 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 until treatment end or until they dropped out. The length of the drug free interval, i.e. 7 days, was added for each subject. Hence, treatment exposure was defined as:
  Treatment exposure = (daylast − dayfirst + 1) + 7 where daylast was defined as the last day of pill intake and dayfirst was the first day of pill intake.
  It should be noted that this time period was calculated regardless of treatment interruptions.

  There were 2 exceptions to this rule:
  1. Treatment exposure after conception was not counted (except the interval of 7 days, which was added for each subject, see above).
  2. Treatment exposure during which additional contraceptive measures (backup contraception) were taken was not counted.

- *Calculation of the Life table analysis (Kaplan Meier estimator)*
  In addition to the calculation of the PI, a survival analysis was performed for the time to the occurrence of a pregnancy in study A15129. The cumulative failure rate, i.e. the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of pregnancies that were considered as 'during treatment'.
  Study A09653 was not considered in the life table analysis since the planned treatment duration was only 7 cycles.

Results

In total, 736 subjects were included in the calculation of the Pearl Index (516 in study A15129 and 220 in study A09653). Since the attributed exposure time was 0 for four subjects, 732 subjects (514 in study A15129 and 218 in study A09653) contributed to the total exposure time. Three pregnancies have been noted during the trials, 1 due to method failure and 2 due to subject failure (non-compliance to the recommended dose-regimen).

On the basis of 12,971 treatment cycles in the ITT- analysis and 12,136 cycles in the Pearl Index-corrected analysis, an overall Pearl Index for typical use (method + patient failure) of 0.31 (upper limit of 95% CI: 0.91) and a Pearl Index for method failure of 0.11 (upper limit of 95% CI: 0.60) was calculated.

In addition to the calculation of the PI, a survival analysis was performed for the time to the occurrence of a pregnancy in study A15129 based on 26 cycles treatment duration. The cumulative failure rate, i.e. the probability of getting pregnant, was calculated using the Kaplan Meier estimator on the basis of unintended pregnancies considered as 'during treatment'. The cumulative failure rate after 2 years of treatment was 0.0044 (95% CI 0.0000 to 0.0105), i.e. the probability of contraceptive protection was 0.9956 (i.e. 99.56%).

Cycle control (bleeding pattern)

Major endpoints included withdrawal bleeding and intracyclic bleeding.
In study A15129, bleeding pattern and cycle control parameters were evaluated as secondary target variables, whereas in study A09653, no distinction between primary and secondary target variables was made.
The methods employed to assess bleeding pattern and cycle control parameters were the same in both studies. In studies A09653 and A15129, the volunteer was to start her bleeding record at the latest with

the onset of regular bleeding at the beginning of the first treatment cycle. The women recorded their bleeding pattern on a diary card.
The bleeding episodes were described using the reference period method recommended by the WHO. The length of the reference period is 90 days. The first reference period was to start on the first day of study medication intake.
A withdrawal bleeding episode during treatment is defined as a bleeding episode which started after the complete or partial treatment withdrawal (i.e., the first episode starting after the last day of treatment intake). Only volunteers with a complete 28-day cycle were considered.
The definition for intracyclic bleeding is based on the definition for withdrawal bleeding. All unexpected bleeding episodes in cyclical treatment regimens were registered as intracyclic bleeding.

Results
The results obtained on percentage of withdrawal- and intercyclic bleeding in the comparative study versus Mercilon® did not indicate clear differences between groups. At 7 months of treatment, the percentage of women with withdrawal bleeding was above 97% with a percentage of intracyclic bleeding of 5-6% in both treatment groups.

Clinical Safety

Six clinical phase II/III studies are included in the Summary of Clinical Safety to prove the safety of Yasminelle. Among these, 2 studies are phase II studies and 4 (including studies A15129 and A09653) are phase III studies. In these phase II/III clinical studies relevant to the safety assessment of Yasminelle, a total of 2096 women were included.

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

Risk assessment of venous thromboembolism
Two cases of venous thromboembolism (VTEs) were reported in 2 women under the age of 25 during the clinical development program of Yasminelle; one case after 4 months and another case after 21 months of treatment. Both cases were reported for Yasminelle-treated women in the course of study A15129 and had been confirmed by diagnostic means and considered possibly and probably related, respectively, to the use of Yasminelle. In another Yasminelle-treated volunteer of study A15129, a thrombosis was initially suspected, but not confirmed by a phlebologist.

In the phase III clinical studies, the overall safety evaluation of Yasminelle included 789 women who were treated for a total of 992 women years (wy). The corresponding incidence rates per 10,000 wy are 30 (95% CI: 6-88) when all cases are considered and 20 (95% CI: 2-73), if only the 2 confirmed cases are taken into account.
As the exposure of Yasminelle-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 can, however, be used as they are based on a much larger data base. It can be safely assumed that Yasminelle, as a lower-dosed product, will not have a higher VTE risk as compared to Yasmin.
For the purpose of the safety assessment of the higher-dosed product Yasmin with respect to the incidence of VTEs, all spontaneous VTE reports received by the company by 6 May 2005 were included in the registration file of Yasminelle. These numbers include all confirmed VTE cases regardless of whether the patient had other significant risk factors in addition to OC use (e.g. obesity, coagulopathies, fractures, immobilisation, surgery).

During the period since first launch (Germany, Nov 2000) through the end of Mar 2005, worldwide exposure to Yasmin was over 119.3 million cycles, which translates into approx. 9.2 million wy of Yasmin use. By 6 May 2005, the spontaneous reporting rate worldwide for VTEs for Yasmin were calculated to be 4.4 VTEs per 100,000 wy. Based on spontaneous reporting, the overall worldwide mortality rate related to VTE among Yasmin users is 0.17 deaths per 100,000 wy.

Additionally, extensive information coming from interim data of two post-marketing studies is available, the EURAS study performed in Europe as part of a post-registration commitment, and the Ingenix study, a post-marketing study performed in the US.
The interim analyses presented up to now indicate that there is no difference in VTE risk between Yasmin and other OC users. The data reported for the Ingenix study are in agreement with the first year incidence rates of venous thromboembolism found for Yasmin and other oral contraceptives in the EURAS study. The results from the EURAS and Ingenix study will be assessed in 2007.

Periodic Safety Update Reports (PSUR) Submission

The PSUR cycle is the same as the PSUR cycle of Yasmin.

Discussion of clinical trial results

Clinical efficacy

**Contraceptive efficacy*
The efficacy of a lower EE dosed Yasminelle can be considered sufficiently proven by the clinical evidence presented:
The results on both Pearl Indices and cumulative failure rate are well within the range of that noted for other monophasic COCs.

Regarding investigational methods applied, the requirements for study size and pregnancy reporting of the Note for Guidance 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 in demography between the women in the Yasminelle and Mercilon® groups, respectively.

**Cycle control (bleeding pattern)*
The cycle control obtained with Yasminelle can be considered comparable with that known for other low-estrogen dosed COCs:
The comparative study performed for this purpose, was considered of adequate design and the choice of the comparator is acceptable as Mercilon® is also a COC with lowered EE dose (20 µg ethinylestradiol + 150 µg desogestrel) but similar progestagen dose that is derived from Marvelon® (30 µg ethinylestradiol + 150 µg desogestrel).

Clinical safety

**Adverse drug reactions*
The pattern of adverse drug reactions (ADRs) observed during treatment with Yasminelle is considered typical for a combined oral contraceptive and did not deviate from that observed in the references group treated with Mercilon®.

**Risk of venous thromboembolism*
Two VTEs were reported during the clinical development program of Yasminelle in a group of 789 women who were treated with Yasminelle for a total of 992 women years (wy).

As the exposure of Yasminelle-treated women in this registration file is far too limited to adequately quantify the risk of rare events such as VTE, the registration file on this point was supplemented with extensive post-marketing data on Yasmin in relation. This is considered acceptable, as it can be safely assumed that Yasminelle, as a lower-dosed product, will not have a higher VTE risk as compared to Yasmin.
The extensive post-marketing data that are available on the higher EE dosed Yasmin can serve as supportive documentation, which did not indicate a higher risk of VTE than observed for other COCs available on the market.

Product information

SPC
The SPC of Yasminelle is in line with the previously approved product Yasmin.

Package leaflet
During the Mutual Recognition Procedure the application for Yasminelle was referred to the CMD(h) for further discussion on the package leaflet.
In the CMD(h) meeting of 25 April 2006 the readability of the proposed package leaflet, and whether it would be understandable to woman, has been discussed. After the CMD(h) meeting agreement was reached on the package leaflet, as included in Module 3 of this Public Assessment Report. The MAH committed to perform a new user consultation in two Member States, amongst France, and adapt the package leaflet taking into account the results of the user tests to ensure that the leaflet is readable and understandable.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The Board has considered the relative benefit/risk ratio of Yasminelle in the indication of oral contraception to be positive.
With an overall Pearl Index for typical use (method + patient failure) of **0.31** (upper limit of 95% CI: 0.91) and a Pearl Index for method failure of **0.11** (upper limit of 95% CI: 0.60), the degree of contraceptive efficacy obtained with Yasminelle falls well within the range of that noted for other monophasic COCs.
The cycle control obtained with Yasminelle can be considered comparable with that known for other low-estrogen dosed COCs, as the results obtained on percentage of withdrawal- and intercyclic bleeding in the comparative study versus Mercilon® did not indicate clear differences between groups.

The pattern of adverse drug reactions (ADRs) observed during treatment with Yasminelle is considered typical for a combined oral contraceptive and did not deviate from that observed in the references group treated with Mercilon®.
As the exposure of Yasminelle-treated women in this registration file is far too limited to adequately quantify the risk of rare events such as venous thromboembolism, the registration file on this point was supplemented with extensive post-marketing data on Yasmin in relation. The extensive post-marketing data that are available on the higher EE dosed Yasmin did not indicate a higher risk of VTE than observed for other COCs available on the market.

Therefore the MEB, on the basis of the data submitted, considered that Yasminelle demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

During the Mutual Recognition Procedure the application for Yasminelle was referred to the CMD(h) for further discussion on the package leaflet. During the CMD(h) procedure agreement was reached on the package leaflet by the Member States involved. The MAH committed to perform a new user consultation in two Member States and adapt the package leaflet taking into account the results of the user tests to ensure that the leaflet is readable and understandable.

The other Member States mutually recognised the Dutch evaluation for the marketing authorisation on 2 May 2006.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	Britisch 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, CMD(h),
COC	combined oral contraceptives
CV	Coefficient of Variation
DRSP	drosperinone
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EE	ethinylestradiol
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OC	oral contraceptives
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PI	Pearl index
PL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	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

Note: The use of other abbreviations has to be avoided, but if considered necessary above mentioned list should be completed.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Type B.III.1a	Updated CEP from an already approved manufacturer	None	11-10-2005	Approval	
Type B.II.b.2a	Addition of a site where batch control/testing takes place	None	31-10-2005	Approval	
Type B.II.b.2c	Addition of a manufacturer responsible for importation and/or batch release	None	31-10-2005	Approval	
Type B.II.e.1.a1	Change in immediate packaging of the finished product	SmPC / PL	17-11-2005	Approval	
Type B.I.b.2a	Minor change in test procedure for starting material	None	21-11-2005	Approval	
Type B.II.f.1	Shelf-life extension (3-4 years)	SmPC	21-11-2005	Approval	
Type B.I.b.1b	Tightening of specification limits of an active substance used in the manufacturing process of the active substance.	None	02-10-2006	Approval	
Type B.I.b.2a	Change in test procedure for active substance, minor changes to an approved test procedure	None	02-10-2006	Approval	
Type B.I.d.1.a2	Extension of the retest period based on extrapolation of stability data not in accordance with ICH/VICH guidelines (*)	None	26-02-2007	Approval	
Type B.II.f.1b	Extension of the shelf life of the finished product as packaged for sale	SmPC / PL	26-02-2007	Approval	
Type A.5	Change in the name and/or address of a manufacturer of the finished product.	None	30-05-2007	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation holder	None	31-10-2007	Approval	
			1-11-2007	Approval	
Type B.II.e.1.a1	Change in immediate packaging of the finished product	SmPC / PL	1-11-2007	Approval	
Type B.III.1a	Updated CEP from an already approved manufacturer	None	2-11-2007	Approval	
Type C.I.4a	Change(s) in the Summary of Product Characteristics and Package Leaflet due to new pharmacovigilance data.	SmPC / PL	7-2-2008	Approval	

Type B.II.c.4b	Change in synthesis where the specifications are affected.	None	2-4-2008	Approval	
Type A.4	Change in the name and/or address of a manufacturer of the drug substance	None	2-4-2008	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation holder	None	30-10-2008	Approval	
Type A.4	Change in the name and/or address of a manufacturer of the drug substance	None	15-1-2009	Approval	
Type B.II.b.2c	Addition of a manufacturer responsible for importation and/or batch release.	None	15-1-2009	Approval	
Type C.I.4a	Change(s) in labelling due to new quality, preclinical, clinical or pharmacovigilance data.	None	15-1-2009	Approval	
Type C.1.2b	Change(s) in the Summary of Product Characteristics of a generic medicinal products following assessment of the same change for the reference product.	SmPC	18-6-2009	Approval	
Type B.II.b.5a	Tightening of in-process limits applied during the manufacture of the finished product	None	17-8-2009	Approval	
Type B.II.d.2d	Other changes to a test procedure (including replacement or addition)	None	17-8-2009	Approval	
Type B.II.b.5a	Tightening of in-process limits applied during the manufacture of the finished product	None	19-8-2009	Approval	
Type B.II.d.2d	Other changes to a test procedure (including replacement or addition)	None	19-8-2009	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation holder	SmPC	11-9-2009	Approval	
Type A.2a	Change in the (invented) name of the medicinal product	SmpC / PL	14-10-2009	Approval	
Type B.II.e.1.a1	Change in immediate packaging of the finished product	SmPC / PL	18-3-2010	Approval	
Type C.I.4	Change(s) in the Summary of Product Characteristics and Package Leaflet due to new clinical data.	SmPC / PL	10-1-2011	Approval	
Type P	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	PL	14-1-2011	Approval	
Type B.II.f.1	Shelf-life extension	SmPC / PL	1-2-2011	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation	SmPC	1-3-2011	Approval	

	holder				
PSUR	Periodic Safety Update	SmPC / PL	24-3-2011	Approval	
Type R	Renewal of the marketing authorisation.	SmPC, Annex II, Labelling and PL	16-6-2011	Approval	
Type C.I.3a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products Implementation of wording agreed by the competent authority	SmPC / PL	20-6-2011	Approval	
Type B.I.b.1b	Tightening of specification limits of an active substance used in the manufacturing process of the active substance.	None	15-7-2011	Approval	
Type B.I.b.1c	Addition of a new specification parameter to the specification with its corresponding test method	None	15-7-2011	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation holder	SmPC	4-8-2011	Approval	
Type A.4	Change in the name and/or address of a manufacturer of the drug substance	None	4-8-2011	Approval	
Type A.5	Change in the name and/or address of a manufacturer of the finished product	None	4-8-2011	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation holder	SmPC	13-10-2011	Approval	
Type A.4	Change in the name and/or address of a manufacturer of the drug substance	None	13-10-2011	Approval	
Type A.5	Change in the name and/or address of a manufacturer of the finished product	None	13-10-2011	Approval	
Type C.I.3a	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products Implementation of wording agreed by the competent authority	SmPC / PL	18-1-2012	Approval	
Type C.I.11b	Introduction of the risk management plan which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required	None	26-1-2012	Approval	
Type	Updated certificate of	None	13-4-2012	Approval	

B.III.1.a.2	suitability from an already approved manufacturer				
Type B.III.1.a.1	New certificate of suitability from an already approved manufacturer	None	15-11-2012	Approval	
Type C.I.4 WS	Adapting section 4.4 and 5.1 of the SmPC of all combined oral contraceptives	SmPC	27-12-2012	Approval	
Type C.I.8	Introduction of a summary of pharmacovigilance system for medicinal products for human use	None	17-4-2013	Approval	
Type C.I.4 WS	Changes to the SmPC section 4.3 and PIL	SmPC / PL	29-4-2013	Approval	
Type B.III.1.a.3	Submission of a new certificate of suitability for a starting material from a new manufacturer	None	27-6-2013	Approval	
Type B.II.b.3.a	Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions	None	27-6-2013	Approval	
Type B.II.b.4.a	Change in the batch size of the finished product up to 10 fold	None	27-6-2013	Approval	
Type B.II.d.1g WS	Change in the specification parameters and/or limits of the finished product, Addition or replacement of a specification parameter with its corresponding test method as a result of a safety or quality issue	None	10-4-2014	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation holder	SmPC	11-6-2014	Approval	
Type C.I.1b WS	Change(s) that are not covered by the defined scope in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	SmPC / PL	30-7-2014	Approval	
Type C.I.11a WS	Change(s) to, the risk management plan, implementation of wording agreed by the competent authority	None	31-10-2014	Approval	
Type B.I.b.2a	Minor change in test procedure for active substance used in the manufacturing process	None	8-12-2014	Approval	
Type B.I.a.3a	Change in batch size, Up to 10-fold increase compared to the originally approved batch size	None	8-12-2014	Approval	

Type B.II.b.3a	Minor change in the manufacturing process of the finished product	None	8-12-2014	Approval	
Type C.I.4 WS	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	SmPC / PL	17-4-2015	Approval	
Type R	Renewal	None	20-4-2015	Approval	
Type C.I.4 WS	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	SmPC / PL	18-8-2015	Approval	
Type C.I.11a WS	Change(s) to, the risk management plan, implementation of wording agreed by the competent authority	None	18-5-2016	Approval	
Type B.III.1.a.2	Submission of a new or updated Ph. Eur. certificate of suitability: For an active substance Updated certificate from an already approved manufacturer	None	4-8-2016	Approval	
Type B.II.b.3a	Minor change in the manufacturing process of the finished product	None	12-9-2016	Approval	
Type P	Minor change to the labelling of the blister packaged in a wallet	PL	16-5-2017	Approval	
Type C.I.4 WS	Change(s) in the Summary of Product Characteristics due to new quality, preclinical, clinical or pharmacovigilance data.	SmPC	22-8-2017	Approval	
Type A.4	Change in the name and/or address of a manufacturer of the drug substance	None	25-9-2017	Approval	
Type A.5	Change in the name and/or address of a manufacturer of the finished product	None	25-9-2017	Approval	
Type B.III.1.a	Submission of a new or updated Ph. Eur. certificate of suitability: For an active substance Updated certificate from an already approved manufacturer	None	25-9-2017	Approval	
Type P	Art. 61(3): Notification related to implementation of the safety features according to the Falsified Medicines Directive 2011/62/EU	None	6-8-2018	Approval	
Type C.I.z	Other variations	SmPC	26-2-2019	Approval	
Type C.I.4 WS	Change(s) in the Summary of Product Characteristics and	SmPC / PL	5-11-2020	Approval	

	Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.				
Type C.I.4 WS	Change(s) in the Summary of Product Characteristics due to new quality, preclinical, clinical or pharmacovigilance data.	SmPC	30-6-2021	Approval	
Type B.II.b.5.b	Addition of a new test(s) and limits applied during the manufacture of the finished product	None	6-7-2021	Approval	

ANNEX I – TYPE II VARIATION NL/H/XXXX/WS/470

I Recommendation

Based on the review of the data on safety, the RMS considers that the variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008 for Yasminelle, Belanette (Aliane), Liofora, Yasminelle 28, Belanette 28 (Aliane 28), Yasmin, Yasmin 28, Ethinylestradiol / Drospirenon 0,03 mg / 3 mg Berlipharm (Yira) and Palandra (ethinylestradiol, drospirenon), indicated for oral contraception, for the following proposed changes: update of the environmental risk assessment (ERA) and SmPC sections 5.3 and 6.6 is approvable.

II Executive summary

II.1 Scope of the variation

The MAH submitted a type II variation for Yasminelle, Belanette (Aliane), Liofora, Yasminelle 28, Belanette 28 (Aliane 28), Yasmin, Yasmin 28, Ethinylestradiol / Drospirenon 0,03 mg / 3 mg Berlipharm (Yira) and Palandra (ethinylestradiol, drospirenon) via the worksharing procedure. The application concerns changes proposed to the ERA and SmPC sections 5.3 and 6.6. The ERA update had been previously the subject of regulatory submissions for the medicinal products YAZ 24+4 and Ethinylestradiol/Drospirenon 24+4 0,02 mg/3 mg Berlipharm authorised via NL/H/1269/MR and NL/H/1270/MR (NL/H/xxxx/WS/157, NL case number: 505979). The procedure ended positively on 28 Apr 2016. With respect to the ERA this means that with this procedure, the ERA of the nine products subject to the current procedure are brought in line with the ERA concluded at April 28, 2016 for Yaz 24+4 via NL/H/1269/MR and NL/H/1270/MR.

The ERA dossier (study reports) of the MAH for both active substances, 17α-ethinylestradiol and drospirenone, is complete and in accordance with EMA guidelines.on ERA.

The ERA in 2016 was finalised with no further questions or commitments after full evaluation of all submitted study reports and data on exposure assessment.

III Scientific discussion

III.1 Quality aspects

N/A

III.2 Non clinical aspects

III.2.1 Environmental risk assessment

Result of new submitted studies
New studies have not been submitted.

Updated ERA
The MAH has submitted an ERA dated November 2015 for the products Yaz, Yaz flex, Yasminelle and Yasmin, covering all MAH's marketed products containing the combination of ethinylestradiol / drospirenone as active substances. This ERA was performed in accordance with EMA guidelines on ERA.

November 2015 means that this ERA has not been updated to cover the final outcome of the variation

procedure concluded at April 28, 2016 (NL/H/xxxx/WS/157) to which reference is made in the MAH's cover letter.

Study reports
Studies on physico-chemical properties, environmental fate and behaviour and ecotoxicology have been evaluated by the RMS in the previous procedure, including study summaries. These are not repeated here. The results of the studies are compiled in the table with environmental endpoints of which the final versions from the 2016 procedure are repeated in the next section.

The RMS has one question with regard to the effect assessment (see Assessor's comment at the end of this section).

Exposure assessment
The exposure assessment performed by the MAH contains combined sales data of all their products containing ethinylestradiol / drospirenone in the EU member states. PEC values for both actives were calculated and compared to the derived PNEC values. After a Tier IIB refinement of the exposure assessment using SimpleTreat, as per EMA guidance, a potential risk was identified for ethinylestradiol in 14 member states and for drospirenone in one member state.

The RMS has one question with regard to the exposure assessment. The submitted dossier was considered to be complete and the ERA and the associated studies adequate. Two points were raised which needed to be considered:

1. The outcome of the fish full life cycle study with drospirenone (study nr. A62532) is a NOEC of <0.23 µg/L, this needs to be properly reflected in the ERA.
2. The exposure assessment is based on 2013 sales data of all MAH's EE2/DRSP marketed products. Sales data from the most recent sales period must be provided to update the ERA.

The outcome of the ERA may change depending on the height of the revised PEC values.

Conclusion on ERA assessment
It is noted that the two tables with environmental endpoints shown below are identical to those from the FVAR of procedure NL/H/xxxx/WS/157 (2016), except for the $PEC_{surface\ water}$. The value for $PEC_{surface\ water}$ may change after sales data used for exposure assessment have been updated.

Summary of main study results for ethinylestradiol

Substance (INN/Invented Name): ethinylestradiol			
CAS-number (if available): 57-63-6			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	4.2	Potential PBT: N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.2	
	BCF_{SS}	517, 881 L/kg_{ww}	normalised to 5% lipids. Conclusion: not B
Persistence	ready biodegradability	not readily biodegradable	
	DegT50, parent, aerobic	$DT_{50\ water}$ = 8.5/25/11 d (r/l/l) $DT_{50,\ system}$ = 51/76/59 d (r/l/l)	r=river; l=lake DT_{50} values corrected to 12°C.

	DegT50, parent, anaerobic	$DT_{50\ water}$ = 26/38 d (r/l) $DT_{50,\ system}$ >212/>212 d (r/l)	r=river; l=lake DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	EC10 = 9 µg/L NOEC ≥387 µg/L NOEC = 0.16 ng/L	T
	CMR	not investigated	
PBT-statement :	Ethinylestradiol is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$. Refined based on sales data	0.205	ng/L	> 0.01 threshold: N
Other concerns (e.g. chemical class)	synthetic estrogen		Y
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} = 3162 L/kg	HPLC method values
Ready Biodegradability Test	FDA 3.11	not readily biodegradable	
Aerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ = 4/12/5.3 d(r/l/l) $DT_{50\ system}$ = 24/36/28 d (r/l/l) % shifting to sediment = 49%, 43%, 50% at day 11.	r=river; l=lake DT_{50} values at 20°C; Significant shifting to sediment observed.
Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ = 12/18 d(r/l) $DT_{50\ system}$ >100/>100 d (r/l)	r=river; l=lake DT_{50} values at 20°C

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *D. subspicatus*	OECD 201	EC10	9	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥387	µg/L	reproduction
Fish, Early Life Stage Toxicity Test/*P.promelas*	OECD 210	NOEC	0.16	ng/L	lowest NOEC from WFD EQS dataset.
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥20,000	µg/L	respiration
Phase IIb Studies					
Bioaccumulation / *L. macrochirus*	OECD 305	BCF_{SS}	372 634	L/kg_{ww} L/kg_{ww}	%lipids: 3.6% BCF based on total radioactivity
Sediment dwelling organism / *C. riparius*	OECD 218	NOEC	≥100	mg/kg_{dw}	1.9% o.c.; emergence development

Conclusions on studies for ethinylestradiol:

$PEC_{surface\ water}$ for ethinylestradiol is below the action limit of 0.01 µg/L, however, due to its estrogenic mode of action an environmental risk assessment is warranted.
Ethinylestradiol is not a PBT, nor a vPvB substance.
A potential risk to the surface water compartment is observed. The risk assessment showed that no risk to the STP, groundwater and sediment compartment is anticipated.
Considering the above data, ethinylestradiol should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

Summary of main study results for drospirenone

Substance (INN/Invented Name): drospirenone					
CAS-number (if available): 67392-87-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	3.08			
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	3.08			
	BCF_{SS}	97 L/kg, 102 L/kg			normalised to 5% lipids. Conclusion: not B
Persistence	ready biodegradability	not readily biodegradable			
	DegT50, parent	$DT_{50,\ water}$ = 12/10 d (r/l) $DT_{50,\ system}$ >214/>214 d (r/l)			l=lake; r=river; DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	NOEC = 1300 µg/L NOEC = 600 µg/L NOEC <0.23 µg/L			T
	CMR	not investigated			
PBT-statement :	Drospirenone is considered to be not PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$. Refined based on sales data	28	ng/L			> 0.01 threshold: N
Other concerns (e.g. chemical class)	synthetic progestin				Y
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} = 6310			HPLC method
	OECD 106	K_{oc} = 754, 767 L/kg			sewage sludge
Ready Biodegradability Test	OECD 301B	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50\ water}$ = 5.9/4.8 d (r/l) $DT_{50\ system}$ >101/>101 d (r/l) % shifting to sediment = 56% and 75% at day 14.			l=lake; r=river; DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**

Algae, Growth Inhibition Test / *S. subspicatus*	OECD 201	NOEC	1300	µg/L	growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	600	µg/L	reproduction
Fish, short term reproduction Test/*P. promelas*	OECD 229 (draft TG)	NOEC	0.7	µg/L	nr. of eggs, nr. of clutches, sexual abnormalities
Fish full life cycle test / *P. promelas*		NOEC	<0.23	µg/L	mortality 7 d larvae
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥9400	µg/L	respiration
Phase IIb Studies					
Bioaccumulation / *L. macrochirus*	OECD 305	BCF_{SS}	94 99	L/kg_{ww} L/kg_{ww}	%lipids: 4.83. BCF based on total radioactivity
Sediment dwelling organism / *C. riparius*	OECD 218	NOEC	≥100	mg/kg_{dw}	1.9% o.c.; emergence development

Conclusions on studies for drospirenone:
Drospirenone is not a PBT, nor a vPvB substance.
A potential risk to the surface water compartment cannot be excluded. The risk assessment showed that no risk to the STP, groundwater and sediment compartment is anticipated.
Considering the above data, drospirenone should be used according to the precautions stated in the SmPC in order to minimise any potential risks to the environment.

III.4 Clinical aspects

N/A

III.5 Overall conclusion and benefit-risk assessment

Environmental risk assessment

The applicant provided an updated ERA. The RMS agrees on the presented calculations of annual consumption, PECs, risk quotients (RQs) and 'FACTOR' and appreciates the adaptations carried forward by the applicant. The RMS also agrees on the use of Fstp = 0.696 by the applicant in their ERA. The RMS agrees on the risk assessment and the statement proposed for the SmPC “Environmental risk assessment studies have shown that ethinylestradiol and drospirenone have the potential of posing a risk to the aquatic environment (see SmPC section 6.6)”. The ERA is considered acceptable.

III.6 SmPC changes

Only the SmPC paragraphs which are altered are displayed, with added text indicated in blue:

5.3 Preclinical safety data

In laboratory animals, the effects of drospirenone and ethinylestradiol were confined to those associated with the recognised pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered as species

specific. At exposures exceeding those in users of Yasminelle, effects on sexual differentiation were observed in rat fetuses but not in monkeys. Environmental risk assessment studies have shown that ethinylestradiol and drospirenone have the potential of posing a risk to the aquatic environment (see section 6.6).

6.6 Special precautions for disposal

This medicinal product may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.