PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Yasmin 28, 0.03/3 mg film-coated tablets

Bayer B.V., Mijdrecht, The Netherlands

drospirenone and ethinylestradiol

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/0217/001/MR
Registration number in the Netherlands: RVG 25413

Date of first revision: 8 March 2010
Date of last revision: 2 August 2021

Pharmacotherapeutic group:	progestagens and estrogens, fixed combinations
ATC code:	G03AA12
Route of administration:	oral
Therapeutic indication:	oral contraception
Prescription status:	prescription only
Date of authorisation in NL:	7 April 2000
Concerned Member States:	DK, ES, FR, IS, NO, SE, UK
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 Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the concerned member states have granted a marketing authorisation for Yasmin 28, film-coated tablets 0.03/3 mg from Bayer BV. The first date of authorisation was on 7 April 2000 in the Netherlands. The product is indicated for oral contraception.

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

The marketing authorisation has been granted based on article 4.8 (a) of Directive 65/65/EEC (i.e. a stand alone dossier or full application).

Yasmin 28 is a combined oral contraceptive that contains 30 μg ethinylestradiol and 3 mg drospirenone. As is the case in other combined contraceptives, the action of Yasmin 28 is mainly based on the inhibition of ovulation. Drospirenone is a new synthetic steroid hormone with progestagenic and slight aldosterone-antagonistic activity, intended for use as the progestagenic component of this combined oral contraceptive.

For the purpose of registration in the Netherlands, a complete file has been submitted in accordance with Directive 65/65/EEC, Article 4.8 (a) (currently article 8(3) of Directive 2001/83/EC). Following national registration, a procedure of mutual recognition (Directive 75/319/EEC) has taken place, with the Netherlands as the reference member state. This procedure was completed on 8 August 2000.

Yasmin 28 is available in calendar packs each containing 21 immediate release tablets (3 mg drospirenone and 0.03 mg ethinylestradiol) followed by 7 placebo tablets (without active substances). The assessment of Yasmin (NL/H/215/001/MR: NL License RVG 23827) also applies to Yasmin 28. One tablet Yasmin is administered daily for 21 days followed by a 7-days tablet-free interval.

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 substance
The active substances are drospirenone and ethinylestradiol. Drospirenone was a novel active substance at the time of initial marketing authorisation, but nowadays is considered an established active substance. Ethinylestradiol is an established active substance, which 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. Drospirenone is manufactured by means of fermentation followed by chemical conversion and purification. The manufacturing process consists of 17 steps.

The Certificate of Suitability Procedure (CEP) 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.

Stability data on the active substances have 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.

** 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
The light yellow tablets consist of 3 mg of the active substance drospirenone and 0.030 mg of the active substance ethinylestradiol. The tablets are round with convex faces.

The 7 white placebo tablets contain the same excipients as the light yellow tablets, but lack the active substances drospirenone and ethinylestradiol.

The excipients are:

Core:	lactose monohydrate, maize starch, pregelatinised maize starch, povidone 25000, magnesium stearate
Coating:	hypromellose 5 mPsec, macrogol 6000, talc, titanium dioxide, yellow iron oxide.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant Ph.Eur. monographs. Yellow iron oxide (E172) complies with the European quality and safety standards.

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.

The aim of the development studies was to develop an oral conventional tablet comparable to the other oral contraceptives marketed by the MAH. No compatibility problems and shelf-life problems have occurred with drospirenone. Following ingestion of the tablet, both active substances are released sufficiently rapidly and no problems with bioavailability have occurred.

Manufacturing process and quality control of the medicinal product
The product is manufactured using conventional manufacturing techniques. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have 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 have 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 have been provided from 3 batches in accordance with applicable European guidelines demonstrating the stability of the product for 3 years. The labelled storage conditions are *"store below 25°C, store in the original package"*.

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

The evaluation of the pharmacological and toxicological data mainly focuses on the new active substance drospirenone and its combination with ethinylestradiol. Sufficient literature is available about the properties of ethinylestradiol. This report does not include a list of references.

Good Laboratory Practice
All pivotal toxicity studies and some toxicokinetic studies have been conducted in accordance with standards of Good Laboratory Practice (GLP).

Pharmacology
The pharmacodynamic properties of the synthetic progestagen drospirenone have been studied both *in vitro* and *in vivo.* Drospirenone has a high affinity for the progesterone receptor. The affinity relative to progesteron is about 40%, and relative to levonorgestrel and gestoden is approximately 33%. Drospirenone also has a high affinity for the mineralocorticoid receptor, but has a low affinity for the androgen- and the glucocorticoid receptor. Drospirenone does not bind to the estrogen receptor nor to the human sex hormone binding globulin and the human corticoid binding globulin.

The following comparisons can be made between drospirenone, cyproteronacetate and spironolacton:

- The progestagen activity of drospirenone is similar to that of cyproteronacetate. The anti-androgen activity of drospirenone is about one-third of that of cyproteronacetate, but 5 to 10 times that of progesterone. The anti-androgen activity does not correlate with the affinity for the receptor.
- The antimineralocorticoid activity of drospirenone is about 6 to 8 times that of spironolactone and is also more potent than the activity of gestoden. In rats, the antimineralocorticoid effects occur in dosages that also prevent ovulation.
- The anti-gonadotropic activity of drospirenone is 20 to 40 times that of spironolactone.

Drospirenone does not have any estrogen, glucocorticoid or anti-glucocorticoid activity.

There are no indications from safety pharmacological studies in laboratory animals for any special effects on the central nervous system, the respiratory or the cardiovascular system.

Pharmacokinetics

Absorption, distribution, biotransformation and excretion

Absorption
Drospirenone is rapidly absorbed from the gastrointestinal tract. In mice and rats a dose-dependent biological availability was found, which increased up to 100% in high dosages. The bioavailiability in rabbits and monkeys was not dose-dependent and lower, 43% and 40-75%, respectively.

Distribution
The plasma-protein binding of drospirenone is high, both *in vitro* (humans, monkeys, rats and rabbits) and *in vivo* (rabbits): 95-97%. Drospirenone is rapidly distributed to the tissues following oral administration. The highest concentrations of drospirenone are measured within two hours in the liver, the stomach, the intestines, the adrenal glands and fatty tissue. In pregnant animals, distribution also occurs to the placenta, the fetus and the amniotic fluid. The elimination of drospirenone from the tissues is comparable to the elimination from the plasma.

Biotransformation
Several metabolites of drospirenone have been identified. The metabolite patterns differed considerably between animal species. As a result of the complexity of the human metabolite pattern, it is difficult to compare the human metabolite pattern with the patterns of other species. The cytochrome P450 system seems to be hardly involved in the degradation of drospirenone. Pharmacokinetic data of mice and rats suggest that the degradation of drospirenone occurs primarily in the plasma, probably as a result of plasma esterases.

Elimination
Elimination experiments with 14C-labelled drospirenone have been carried out in rats, mice, rabbits and monkeys. The major part of the drospirenone dose was excreted in the faeces (mice and rats 70-90%, rabbits 50%, monkeys 60%) and a minor part in the urine (mice and rats 5-14%, rabbits 40%, monkeys 20%). Elimination in mice, rats and rabbits was complete in 2-4 days, whereas in monkeys elimination was 15-20 days. No data are available about elimination in the bile and in breast milk in animals.

Toxicology

Toxicity following repeated administration
After exposure of rats, mice, and monkeys to drospirenone alone, pharmacodynamic effects on the sex organs and interruption of the estrus cycle were found. Other findings included increased body weight, reduction of the relative weight of the adrenal gland, changes in the carbohydrate, fat and protein metabolism, increased urine volume and increased sodium and potassium excretion.

Following exposure to the combination of ethinylestradiol and drospirenone the weight of the liver and the pituary gland increased and the ovary weight decreased. All types of blood cells were reduced in number. Histological changes in reproductive organs, increased proliferation of mammary gland tissue and hyperplasia of the adrenal glands were observed.
Moreover, a dose-dependent increase in heartrate after treatment with ethinylestradiol and the combination of drospirenone and ethinylestradiol was determined in monkeys.

At the lowest combined dose of 0.003 mg ethinylestradiol and 0.3 mg drospirenone per kg body weight in rats, histological changes of the sex organs and some effects on other haematological and biochemical parameters were observed.

Reproduction toxicity
In a full series of reproduction studies, the effects of drospirenone, ethinylestradiol and the combination of drospirenone and ethinylestradiol on fertility and early embryonic development (rats), embryonic and fetal development (monkeys) and pre- and post-natal development (rats) have been studied.
Embryotoxicity studies in rats and rabbits have only been carried out with drospirenone, as ethinylestradiol is embryolethal in these animals. No significant malformations were found in the different dosing groups following exposure during organ development.

Drospirenone, administered without ethinylestradiol, was fetotoxic in rats. During combined exposure to drospirenone and ethinylestradiol, the estrus cycle was disturbed and fetotoxicity was observed. Exposure to drospirenone with ethinylestradiol in the final phase of gestation resulted in effects on the sex differentiation of male and female rat fetuses, but this was not the case in monkey fetuses. During pre/post natal exposure, reduced fertility of offspring was observed apart from fetal toxicity. The reported effects on reproduction were found at an exposure that was comparable to the exposure in humans during normal use of Yasmin 28.

Mutagenity
The following *in vitro* tests were carried out to investigate the mutagenity of drospirenone:
- the Dames gene mutation test with *Salmonella typhimurium* and *E.coli;*
- the HGPRT gene mutation test in V79 eukaryote cells;
- the chromosome aberration test in human lymphocytes;
- UDS (Unscheduled DNA repair Synthesis) test in primary hepatocytes in rats;
- DNA adduct formation in human liver tissue;
- DNA adduct analysis in female rat hepatocytes;
- evaluation of the clastogenic potential of drospirenone in human peripheral blood lymphocytes.

Drospirenone shows interaction with DNA in the liver of mice (carcinogenity study) and rats (UDS test). However, based on the absence of DNA adduct formation in the human liver and the negative results of the other mutagenity studies, mentioned above, it was concluded that there is no proof for any mutagenity of drospirenone.

Carcinogenity
Two carcinogenity studies were carried out in female mice and rats, with drospirenone, ethinylestradiol and the combination of these two substances. No clear differences were found between rats and mice. Following exposure to ethinylestradiol and the combination of ethinylestradiol and drospirenone the incidence of pituary gland adenoma, adenocarcinoma of the uterus, breast cancer and hepatic adenoma increased. The effects after combined exposure were slightly weaker. Exposure to drospirenone alone did not result in an increase in the number of tumour cells compared to the control group. The observed increased incidence of the above-mentioned tumours is a known effect of ethinylestradiol in rodents and is the result of a physiological effect of estrogens that is not observed in humans. Based on the progestative properties of drospirenone, it was expected that drospirenone would reduce this effect. The carcinogenity studies did not provide any evidence of a carcinogenic risk for the use of Yasmin 28 in humans.

Environmental risk assessment
Yasmin 28 has been authorised in 2000, which is before Directive 2001/83/EC came into force. Therefore it was not required to perform an environmental risk assessment for Yasmin 28.

II.3 Clinical aspects

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

Indication and properties of the product
Yasmin 28 is a monophase oral contraceptive combination of an estrogen and a progestagen. The new synthetic progestagen drospirenone, a testosterone derivative, has both progestagenic properties and mild anti-androgenic and antimineralocorticoid activity in preclinical experiments. It has been investigated whether these properties also become apparent in clinical trials.

Evaluated clinical studies
The registration file includes 10 pharmacodynamic, 11 pharmacokinetic and 12 clinical studies. Contraceptive efficacy was documented in 9 Phase II/III studies. These include 7 comparative and 2 non-comparative studies.
Two comparative studies can be considered the most important (pivotal) studies. Moreover, 3 studies have been carried out of which the results have not been included in the analysis of contraceptive efficacy. Two studies investigate the effects on acne and one study investigates the symptoms of premenstrual syndrome.

Pharmacodynamic properties

Dose-response studies pertaining to the inhibition of ovulation and the inhibition of the remaining ovarian activity.
A Phase I study of the ovulation inhibiting action of drospirenone 0.5, 1, 2, or 3 mg daily, without concomitant administration of ethinylestradiol, revealed that 2 mg is the lower limit for ovulation inhibition. In order to determine the optimum dosage of drospirenone in combination with ethinylestradiol, the combination of drospirenone 2 mg and ethinylestradiol 30 μg was compared to drospirenone 3 mg and 30 μg ethinylestradiol. A dosage of 4 mg drospirenone did not result in further inhibition of ovulation. On the basis of these results, the dosage of 3 mg drospirenone was selected for further investigation. At this dosage, no ovulation was demonstrable, whereas in 9% of the patients ovarian activity (follicle maturation) could be established. Adequacy of ovulatory inhibition of the doses selected for further investigation is considered sufficiently demonstrated.

Anti-mineralocorticoid properties
Experimental animal research and Phase I studies in men indicated that drospirenone in high dosages (15-60 mg) also has anti-mineralocorticoid (anti-aldosterone) properties. The anti-mineralocorticoid effect of drospirenone is due to competitive inhibition for the binding of aldosterone to the mineralocorticoid receptor. The anticipated clinical effects include an increase in sodium excretion and a reduction of the potassium excretion in the urine. In small groups of women extensive Phase I studies have been performed to investigate the clinical effects of these anti-mineralocorticoid properties at a much lower dosage of 3-4 mg drospirenone, used for the inhibition of ovulation, with or without ethinylestradiol.
The studied combinations of drospirenone and ethinylestradiol were 2 mg/30 μg, 3 mg/30 μg, 3 mg/20 μg, 3 mg/15 μg and 4 mg/30 μg. The combinations levonorgestrel 150 μg/ethinylestradiol 30 μg (Microgynon) and desogestrel 150 μg/ethinylestradiol 30 μg (Marvelon) were also used. The treatment periods varied from 3 to 13 cycles.

Different dosages of drospirenone show a dose-related increase in plasma renin substrate (angiotensinogen), plasma-renin activity and plasma aldosterone. The effects on angiotensin II and renin are less outspoken. The urinary excretion of aldosterone metabolites and free aldosterone increased with

the drospirenone dose. With the exception of an increase in plasma renin substrate (an estrogen-related effect) these effects were not seen during treatment with the reference preparations levonorgestrel and desogestrel.

The sodium and potassium plasma levels remained almost unchanged during the treatment period. During the first treatment cycle, a dose-dependent initial increase in the excretion of sodium in the urine up to the second half of the cycle was observed. The excretion reached steady state in the second half of the cycle. During the first treatment cycle, a dose dependent initial reduction in potassium excretion in the urine occurred, but this remained at a constant level during the second half of the cycle. No marked influence of the ethinylestradiol dose was seen on these effects. After the end of treatment, the values of the RAAS (renin-angiotensin-aldosterone system) returned to their baseline values within a few days. Significant changes in blood pressure, heart rate and body weight were not observed.

Pharmacokinetic properties

The submitted pharmacokinetic studies mainly concern drospirenone, as the pharmacokinetic properties of ethinylestradiol, the other component of Yasmin 28, are considered well-known. However, measured ethinylestradiol plasma levels have been included in the registration file.

Absorption
Following oral administration, drospirenone is completely absorbed, as becomes apparent from the equal amounts of unchanged drospirenone in the urine after both oral and intravenous administration. Only small amounts of drospirenone are retrieved in the faeces after oral administration. The absolute bioavailability is about 80%, illustrating a low impact of the first-pass effect.

Food does not affect the extent of bioavailability of drospirenone, but the bioavailability of ethinylestradiol was reduced by approximately 35%, whereas the maximum concentrations were reduced by 50%.

Distribution
The apparent distribution volume of drospirenone was determined following administration of 14C-labelled drospirenone and estimated at about 3.7 l/kg in steady state. The protein binding of drospirenone was studied *ex vivo* during 3 cycles, also in the presence of several doses of ethinylestradiol. These studies showed that the free fraction is about 3-5%, drospirenone does not bind to Sex Hormone Binding Globulin (SHBG) or Corticoid Binding Globulin (CBG), and concomitant administration of ethinylestradiol does not affect protein binding.

The passing of drospirenone into breast milk was measured after a single oral dose of 3 mg drospirenone with 30 μg ethinylestradiol. The milk/serum-ratio of drospirenone increased during the first 4 hours to a maximum of 0.57. Thereafter, the ratio decreased to an average of 0.16 24-hours after administration. This study showed that the infant is exposed to a maximum of 0.6% of the dose through breast feeding (about 18 μg daily).

Metabolism and excretion
Drospirenone is almost completely metabolised and only small amounts of unchanged drospirenone are detected in the urine and faeces. The cytochrome P450 system is not involved in the metabolism. At least 20 metabolites are formed. The metabolism pattern is almost identical following intravenous and oral administration. After administration of 14C-labelled drospirenone, almost all radioactivity was detected within 10 days.

Pharmacokinetic characteristics
The pharmacokinetic process is biphasic both after intravenous and oral administration of drospirenone to young women. The distribution half-life is about 1.9 ± 1.1 hours and the elimination half-life is about 29.3 ± 12.0 hours.

Total body clearance was 1.5 ± 0.2 ml/min/kg and the apparent volume of distribution was 3.7 ± 1.2 l/kg. The pharmacokinetic units of drospirenone were rather consistent in the 9 studies submitted (based on single dosages).

The pharmacokinetic properties after repeated administration were studied in healthy female volunteers during 1 to 13 cycles. The dose regimen was a combination of drospirenone and ethinylestradiol for 21 days, followed by a treatment-free period of 7 days. The amounts of drospirenone used were not the same in all studies, but varied from 2 to 4 mg daily.
The maximum concentrations of drospirenone (C_{max}) were found 1 to 2 hours after administration. After the maximum was reached, the concentrations dropped with half-lifes of 25 – 33 hours. The time required reaching maximum concentrations and the elimination half-life were similar to those found after single-dose administration. A good correlation was observed between the C_{max} and the AUC following administration of different dosages, which is indicative for linear pharmacokinetic properties of drospirenone. The accumulation factor of the AUC was approximately 2.5 after 3 cycles, and approximately 4 after 6 or more cycles. The maximum concentration increased by a factor of 2 after repeated administration. The trough concentration of drospirenone in plasma increased during daily oral administration and reached a steady state value of approximately 15 ng/ml after the 7^{th} dose.

Concomitant administration of different amounts of ethinylestradiol did not have any influence on the drospirenone plasma levels after single and repeated administration.

Interactions
The influence of the concomitant administration of ethinylestradiol on the pharmacokinetic properties of drospirenone was studied in 18 healthy women; 3 mg drospirenone was administered, alone or in combination with 30 μg ethinylestradiol. No differences were found in the pharmacokinetic parameters between the two dosage regimes. Repeated-dose studies did not reveal differences in trough levels or in the protein-binding of drospirenone after the concomitant administration of 15, 20 or 30 μg ethinylestradiol with 3 mg drospirenone.

The inhibition by drospirenone of several cytochrome P450 systems, namely CYP1A1, CYP2C9, CYP2C19 and CYP3A4, was studied *in vitro*. The determined inhibition values were all at least 40 times higher than the maximum concentrations of drospirenone after repeated administration.

In one study the influence of drospirenone on the kinetic properties of omeprazole was investigated. Omeprazole is metabolised by CYP2C19 and CYP3A4. No statistically significant differences were found in the pharmacokinetic properties of omeprazole and its metabolites following omeprazole administration with or without drospirenone. In view of this finding no *in vivo* interaction studies were considered necessary.

Special patient groups
No studies have been carried out in special patient groups, such as patients with renal or hepatic insufficiency, with the exception of a study in patients with moderate renal insufficiency. As only 1% of the drospirenone dose is cleared unchanged renally, it is not likely that renal insufficiency will lead to a significant increase in drospirenone levels. Preliminary data of the above-mentioned kinetic study confirm this conclusion. However, severe renal insufficiency and acute renal failure are contraindicated due to the mild anti-mineralocorticoid effects of drospirenone.
In relation to hepatic insufficiency, it should be noted that after administration of Yasmin 28 the impact on the liver will be considerable, as is also the case with other steroid hormones. A study in volunteers with hepatic insufficiency is not ethically justified, as this may lead to saturation of the metabolic processes in the liver. Current or previous history of severe hepatic disease is therefore contraindicated. The limited population-pharmacokinetic analysis shows that the influence of body weight on the kinetic properties of drospirenone will be mild.

Efficacy

The table below presents an overview of the relevant studies (Phase II and Phase III). All clinical studies focused on contraceptive efficacy, safety and bleeding pattern. All other endpoints are also indicated in the table.

Phase II and III clinical efficacy and safety studies

Study	Design	n	Treatment	Reference	Cycles	Pharmacology/ Specific safety
AM90 NL,CH, B 1995-97	NV Phase III	40	3 mg DRSP/EE 30 μg		13	Endometrial histology
AI98 D 1993-94	NV Phase III	13	3 mg DRSP/EE 30 μg		13	Tolerability Pharmacokinetic properties
A187 NL,CH, B,D 1990-92	O,R,P Phase II	200 50/group	3 mg DRSP/EE 30 μg 3 mg DRSP/EE 20 μg 3 mg DRSP/EE 15 μg	150 μg LNG/EE 30 μg (Microgynon)	6	BW, BP Pharmacokinetic properties
AJ06* NL,D,B, F,LU, PT,CH 1993-96	O,R,P Phase III	2069 Yasmin 1657 Marvelon	3 mg DRSP/EE 30 μg	150 mg DSG/EE 30 μg (Marvelon)	13	
AI51* B,NL,D 1992-96	O,R,P Phase III	887 Yasmin 442 Marvelon	3 mg DRSP/EE 30 μg	150 μg DSG/EE 30 μg (Marvelon)	26	
AE91 NL 1992-93	O,R,P Phase II	100 25/group	3 mg DRSP/EE 30 μg 3 mg DRSP/EE 20 μg 3 mg DRSP/EE 15 μg	150 μg DSG/EE 30 μg (Marvelon)	6	Haemostasis
AG44 NL 1993-94	O,R,P Phase III	60 30/group	3 mg DRSP/EE 30 μg	150 μg DSG/EE 30 μg (Marvelon)	13	RAAS Haemostasis
AL84 B 1994-97	O,R,P Phase III	60 30/group	3 mg DRSP/EE 30 μg	150 DSG/EE 30 μg (Marvelon)	13	Lipid metabolism Carbohydrate metabolism
AW06 B 1990-91	DB,R, P Phase II	80 20 per group	3 mg DRSP/EE 30 μg 3 mg DRSP/EE 20 μg 3 mg DRSP/EE 15 μg	150 μg LNG/EE 30 μg (Microgynon)	6	RAAS Electrolytes Lipid metabolism Carbohydrate metabolism

*: pivotal studies
NL = Netherlands, B = Belgium, CH = Switzerland, PT = Portugal, LU = Luxemburg, D = Germany
NV = not comparative; O = open; R = randomised; DB = doubleblind; P = parallel; n = number of users; DRSP = drospirenone; EE = ethinylestradiol; RAAS = renin-angiotensin-aldosterone system; BW = body weight; BP = blood pressure

Seven out of the 9 'contraception' studies had a comparative design. Two studies compared Yasmin to Microgynon 30 (150 microgram levonorgestrel + 30 microgram ethinylestradiol), whereas the other studies compared Yasmin to Marvelon (150 microgram desogestrel + 30 microgram ethinylestradiol). All comparative studies were randomised and of open-label design, with the exception of the metabolic study which used a double-blind design to investigate the combination of drospirenone and ethinylestradiol in

different dosages on the lipid and carbohydrate metabolism and the RAAS (renin-angiotensin-aldosterone system).
Clinical-pharmacological tests were carried out in several studies. Five studies were also designed to study the specific safety of Yasmin in relation to effects on haemostasis, RAAS, lipid- and carbohydrate-metabolism, and endometrium.

Additionally, the clinical relevance of the mild antimineralocorticoid effects of Yasmin on body weight and the symptoms of premenstrual syndrome has been studied. Further, the clinical impact of the mild anti-androgen effects of Yasmin in the treatment of acne and seborrhoea were investigated in two comparative studies. These three studies were not included in the table above.

Inclusion criteria
Healthy, menstruating women between 18 and 35 years of age were included; *de novo* or earlier contraceptive pill users, who were prepared to use another contraceptive method than condoms as AIDS prophylaxis. The women were also prepared to fill in a diary to describe their bleeding pattern.

Exclusion criteria
The main exclusion criteria were pregnancy and lactation, abortion, childbirth or lactation less than one month before, hepatic disease, vascular disease (thrombo-embolic disorder or a history or a positive family history), coagulation disorders, breast- and endometrium-carcinoma, hypertension and medicinal treatment of premenstrual syndrome.

Contraception

The contraceptive efficacy was analysed by means of the Pearl Index (= 13 x number of documented pregnancies x 100/number of treatment cycles). All treatment cycles in which at least 19 tablets of the 21 tablet pack were taken were included in the denominator. The numerator included all pregnancies during treatment (at least one tablet was taken during the cycle in which conception had occurred). For the corrected Pearl Index calculation, cycles in which condom use was documented were not included in the numerator.
A total of 2,274 women have received Yasmin over study periods between 6 and 26 cycles, i.e. a total of 30,110 cycles. Thirteen pregnancies had occurred during the taking of Yasmin. The table below shows an overview of the contraceptive efficacy:

Contraceptive efficacy

	Pearl Index			
Treatment	n*	Cycles	Pregnancies	Pearl Index
DRSP/EE 3 mg/30 microgram	2,274	30,110	13	0.56***
DSG/EE 150 microgram/30 microgram	929	15,096	5	0.43***
	Corrected Pearl Index			
Treatment	n*	Cycles	Pregnancies	Pearl Index
DRSP/EE 3 mg/30 microgram	2,263	29,735	13	0.57 (upper limit 95% CI: 0.90)**
DSG/EE 150 microgram/30 microgram	926	926	5	0.43 (upper limit 95% CI: 0.91)**

* number of users, ** 95% confidence interval *** 95% confidence interval not calculated
DSG = desogestrel, DRSP = drospirenone, EE = ethinylestradiol

The contraceptive action of Yasmin is reversible; within three months after termination of the treatment 95% of the women had a normal menstrual period cycle.

Bleeding pattern

The women recorded their bleeding pattern in a diary. Intramenstrual blood loss was defined as spotting (mild intramenstrual blood loss) or breakthrough bleeding (normal to excessive intramenstrual blood loss). Cycles in which irregular tablet intake occurred, were not included in the analysis. In these cycles more than one tablet was forgotten or the pill-free period lasted shorter than 6 or longer than 8 days.

Phase II studies of different dosages of ethinylestradiol (15, 20 or 30 microgram) combined with 3 mg drospirenone showed a dose-dependent decrease in intramenstrual blood loss with an increasing dosage of ethinylestradiol. The incidence of amenorrhoea was low, but increased with a lower dosage of ethinylestradiol. On the basis of these results, it was concluded that drospirenone 3 mg in combination with 30 microgram ethinylestradiol provided the best cycle control.

Adequate cycle control was confirmed in the pivotal comparative studies (Phase III) with Marvelon as the reference preparation. No significant differences were reported between Yasmin and Marvelon with regard to the incidence of intramenstrual blood loss, amenorrhoea and withdrawal bleeds. The incidence of intramenstrual blood loss decreased with the duration of the treatment, to less than 10%. The incidence of withdrawal bleeds was almost 100%.

Anti-androgenic effects

Acne and seborrhoea
Preclinical studies showed drospirenone to have mild anti-androgenic activity of about one-third of the anti-androgenic activity reported with cyproteronacetate. In order to study the clinical relevance of this finding, an experimental study was performed in which the efficacy of Yasmin was compared to Marvelon with regard to acne and seborrhoea. In both treatment arms a favourable effect was seen on the number of acne lesions. There were no clear differences between both treatment arms. Moreover, Yasmin was compared to the combination of 2 mg cyproteronacetate and 35 μg ethinylestradiol (Diane-35, registered in the Netherlands for the hormonal treatment of acne and seborrhoea). Applying an equivalence limit of 25%, no differences between treatment groups were noted (see also "Discussion on clinical aspects/Special claims").

Anti-mineralocorticoid effects

Body weight
The subjects were asked to measure and record their body weight on a weekly basis in both pivotal contraception studies. These studies showed a minor, but significant reduction in body weight in favour of Yasmin. The difference between the two averages at the end of the 13th treatment cycle was 0.86 kg (95% CI: 0.61-1.12 kg).

Premenstrual syndrome
The efficacy of Yasmin (in 15 users) in the treatment of premenstrual syndrome (PMS) was compared to that of Microgynon (in 13 users) over a period of 3 treatment cycles. The results did not show any differences between the two treatment groups.

Safety

An integrated analysis of the safety data was carried out on data from 2,991 users of drospirenone + ethinylestradiol and 1,123 users of reference preparations (Marvelon and Microgynon).

A total of 2,328 women was treated for 6 months, 1,777 for 13 months and 313 for 26 months. Almost half of the women was between 18 and 25 years of age and 52% of the women had used an oral contraceptive before. The 'body mass index' (BMI) was less than 20 in 24% of the women, between 20 and 25 in 62% of the women and above 30 in 8% of the women.

Adverse events

One woman died due to heart failure probably as a result of severe myocarditis following streptococcal infection.

Menstrual disorders, headache, intermenstrual blood loss, nausea, painful breasts, increase in body weight, acne and migraine were the most frequent reasons (incidence of 1% or lower) for discontinuation as a result of an adverse event. From the perspective of the anti-mineralocorticoid properties it can be stated that two women discontinued treatment because of a decrease in blood pressure and two because of an increase in blood pressure. For one woman a decrease in body weight was a reason to stop. Four women reported a serious adverse event that was possibly related to the use of Yasmin. These adverse events were hypacusis secondary to otosclerosis, cholecystectomy with suspected pulmonary embolism, uterus myoma and generalised pruritis with skin abnormalities.
The most frequent (>1%) mild adverse events of Yasmin included headache, menstrual disorders, painful breasts, nausea, vaginal moniliasis, diarrhoea, depression, leucorrhoea and acne. No marked differences were observed in the pattern of undesirable effects between Yasmin and the various reference preparations.

Specific safety aspects

Effects on the endometrium
Endometrial histology of endometrial biopsies, taken in the 6th or 13th treatment cycle, showed the endometrium to be atrophic or inactive in most cases. Ultrasound evaluations showed a reduction in endometrium thickness to less than 4 mm, on average.

Renin Angiotensin Aldosterone System
A dose-dependent increase in plasma renin substrate (angiotensinogen) was observed in a Phase II study investigating the influence of the ethinylestradiol dosage on the antialdosterone effect of drospirenone. This dose-dependent increase due to stimulation by estrogen was also observed in the reference preparation Microgynon. Additionally, pharmacodynamic studies in all combinations of ethinylestradiol and drospirenone showed an increase in plasma-renin activity and in plasma-aldosterone, while in plasma levels of K^+, Na^+ and creatinine hardly any change was noted. In two pivotal contraception studies routine determinations of plasma K^+, Na^+ and creatinine did not reveal any marked differences between Yasmin and the reference product Marvelon. Clinically relevant effects on the vital signs, in particular blood pressure, have not been observed.

Effects on haemostasis
The effects on the haemostasis parameters have been evaluated in two comparative studies versus Marvelon; in one of these studies also a comparison was made to 3 mg drospirenone in combination with 20 and 15 microgram ethinylestradiol. The comparative studies showed an increase in both coagulation stimulating parameters (fibrinogen, factor VII and thrombin-antithrombin III complexes) as well as fibrinolytic system parameters, without any marked differences between the two treatment groups. As regards the different dosages of ethinylestradiol no more than a tendency towards a smaller effect was reported at a lower dosage.
One case of suspected pulmonary embolism with a possible relationship to the taking of Yasmin was reported. The MAH committed to start a large post-marketing safety study, in which, among others, the incidence of venous thromboembolism (VTE) will be followed. Moreover, the MAH committed to carry out a further haemostasis study after the registration.

Carbohydrate and lipid metabolism
As regards the effects on the lipid metabolism, consisting mainly of estrogen-mediated effects on the HDL and triglycerides, no clear differences were observed between Yasmin and Marvelon. The same applies to glucose tolerance, which decreased slightly in both treatments.

Exposure during pregnancy and breastfeeding
During the clinical studies there were 13 pregnancies. In 11, the pregnancy outcome is known; nine healthy children were born, one child had oesophageal artresia and one child had a suspected coarctatio aortae. No information is available with regard to exposure during the lactation period.

Discussion on clinical aspects

With regard to the assessment of the balance between the efficacy and safety of Yasmin 28 the same criteria apply as those applicable to other hormonal contraceptives, as laid down in the "*Note for Guidance on Clinical Investigation of Steroid Contraceptives in Women*" (CPMP/EWP/519/98). This guideline states that the Pearl Index is primarily indicative for the efficacy of a new hormonal contraceptive. The methodology is another important factor. The submitted documentation complied with the recommendations contained in this European Note for Guidance:

- The number of women included in the studies, the number of treatment cycles studied and the duration of the studies were sufficient;
- A comparative study to assess the adverse events and bleeding pattern has been performed;
- The pivotal studies were carried out in a sufficiently representative study population;
- The calculation of the Pearl Index was based on the women's daily updated diaries, which is considered a reliable method for the registration of compliance;
- The difference between the point estimate (the Pearl Index) and the upper limit of the 95% confidence interval did not exceed 1.

The contraceptive efficacy of Yasmin, with an ITT Pearl Index (pregnancies based on patient + method failure) of 0.57 and an upper limit of the 95% confidence interval of 0.90, is in the same order of magnitude as the efficacy calculated for the reference product Marvelon. The Pearl Index for pregnancies that can only be attributed to the method (Pearl Index for 'method failure') was only 0.09. With regard to the safety, the "Note for Guidance" recommends that for a new hormonal contraceptive the safety information of at least 400 women who have completed one year of treatment has to be submitted. Clinical studies for registration purposes of a medicinal product, however, usually include too few women to provide information on rare risks such as cancer, cardiovascular adverse events and venous thromboembolism. Comparative pharmacodynamic data could indicate possible differences between products, but no generally accepted surrogate endpoints exist for the risk of cancer, cardiovascular adverse events or venous thromboembolism. The Dutch SPC-texts of oral contraceptives include extensive warnings with regard to these rarely occurring risks and the contra-indications have been adjusted accordingly. Although the information on these risks involved in the taking of Yasmin is limited, the clinical dossier does not include indications that the risk profile differs from the risk profile of other, already registered, oral combined contraceptives. The MAH committed to carry out further studies on haemostasis and the incidence of venous thromboembolism.

Special claims
Several studies have been performed to evaluate clinical relevance of the mild anti-mineralocorticoid and anti-androgen properties of drospirenone. With regard to the claim 'anti-mineralocorticoid properties that might be favourable in women suffering from hormone related oedema formation and associated symptoms', documentation is provided by the two pivotal contraception studies. In these studies, the women were asked to measure their body weight on a weekly basis. In both studies, a minor but

significant decrease in body weight was reported in favour of Yasmin. The difference between the two averages at the end of the 13th treatment cycle was 0.86 kg (95% CI: 0.61-1.12 kg). However, as no inclusion criteria had been applied with the aim to select only women with hormone-related oedema formation and associated symptoms, it was not possible to assess the clinical relevance of these results for this patient group.

With regard to the claim 'anti-androgen properties that are favourable for women with acne and seborrhoea' an explorative study was carried out in comparison with Marvelon. Both groups showed a decrease in acne lesions. The study was too small to be able to detect differences between the two treatment groups. Besides, Yasmin was compared to Diane-35 (registered for the hormonal treatment of acne and seborrhoea). On the basis of the selected equivalence limit of 25%, it was concluded that the efficacy of Yasmin did not differ from that of Diane-35. However, this study considered differences in therapeutic effect of up to 25% as not clinically relevant. The documentation was considered insufficient to justify an additional indication.

With regard to an effect on symptoms of premenstrual syndrome (PMS) it has been concluded that the documentation submitted is too limited to adequately assess a clinical benefit in terms of any improvement of PMS on the basis of anti-mineralocorticoid properties.

On the basis of these studies, it can be concluded that a therapeutic dosage of drospirenone also has anti-androgen and mild anti-mineralocorticoid properties. Considering the extent of the data, it can be stated that the clinical studies indicate that the mild anti-mineralocorticoid properties of Yasmin 28 result in a mild anti-mineralocorticoid effect.

Product information

Summary of Product Characteristics

The Summary of Product Characteristics (SPC) text was adjusted to the Dutch SPC text of oral combined contraceptives as harmonised in 1997 in cooperation with the MAHs.

During the European mutual recognition procedure, the SPC text was slightly altered. The recommendation on switching to Yasmin 28 from another contraceptive is now to start using the new tablet after the usual pill-free days, and no longer preferably immediately after the last active tablet. The list of benefits apart from protection against pregnancy in the section "Pharmacodynamic properties" has been shortened. The nationally agreed text in the section "Warnings and precautions" in relation to the increased risk of thrombosis has been replaced by the text agreed with a number of European countries within the framework of a recent procedure of mutual recognition for another oral contraceptive.

Besides, a number of Yasmin 28-specific comments have been included, which are related to the mild anti-mineralocorticoid (anti-aldosterone) properties of drospirenone. Clinically relevant anti-aldosterone effects are expected at a dosage of 10-15 mg drospirenone daily. Therefore, anti-mineralocorticoid effects at a dosage of 3 mg will only be limited. There are, however, situations and disorders that increase plasma level of drospirenone, or an increased effect as a result of the concomitant use of medicinal products that influence the electrolyte balance. Information about the concomitant use of these types of medication such as ACE-inhibitors, angiotensin-II-receptor antagonists, aldosterone antagonists, potassium sparing diuretics or NSAIDs is not available. Besides, an anti-mineralocorticoid effect may be expected in patients with electrolyte excretion disorders. Therefore, Yasmin 28 is contra-indicated in patients with severe renal insufficiency or acute renal failure. Moreover, a warning has been included stating that in the event of the concomitant use of the above-mentioned medication the plasma potassium level must be monitored.

Finally, a comment has been included in the section 'Pharmacodynamic properties' stating that the clinical studies indicate that the mild anti-mineralocorticoid properties result in a mild anti-mineralocorticoid effect.
No comments have been included with regard to an effect on premenstrual syndrome, acne and seborrhoea due to insufficient clinical proof.

Any effects of accidental exposure to Yasmin during pregnancy cannot be assessed on the basis of the limited information available. The comments with regard to unintended use during pregnancy have been adjusted to this and combined with information from public literature. Extensive epidemiological studies have not been able to demonstrate an increased risk of congenital abnormalities in children of mothers, who have used an oral contraceptive in the period preceding pregnancy. Neither are there any indications for teratogenous abnormalities in cases in which a progestagen-containing contraceptive was used without the user knowing she was pregnant. Although this probably applies to all oral contraceptives, it is not known whether this also applies to Yasmin 28.
About 0.6% of the orally administered dose of drospirenone in conjunction with ethinylestradiol is excreted in the breast milk. The possible effects of this have not been studied. Therefore, a general text applicable to all oral contraceptives has been added to the SPC text.

Package leaflet
At the time of marketing authorisation of Yasmin 28 it was not yet required to have a harmonsied proposal for the package leaflet and labelling. Therefore, no package leaflet was established during the initial procedure for mutual recognition. The package leaflet has been harmonised later during a type II variation which ended on 31 August 2006.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Yasmin 28 is available in calendar packs each containing 21 immediate release tablets (3 mg drospirenone and 0.03 mg ethinylestradiol) followed by 7 placebo tablets (without active substances). The assessment of Yasmin (NL/H/215/001/MR: NL License RVG 23827) also applies to Yasmin 28.

Chemical-pharmaceutical information
Yasmin 28 is available as conventional film-coated tablets and contains common excipients. The product's shelf life is 3 years in the commercial packaging at a temperature not exceeding 25°C. 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. There is one outstanding issue for which the MAH has provided a commitment (see below). This issue can be dealt with post approval.

Preclinical data
Considerable information about ethinylestradiol is available from literature. In particular, the properties of drospirenone and its combination with ethinylestradiol are discussed.

Experimental-pharmacological data show that drospirenone has a high affinity for the progesterone- and mineralocorticoid receptor and a low affinity for the androgen and glucocorticoid receptor. Animal experiments showed anti-androgen and anti-mineralocorticoid activity of drospirenone, but no estrogen, glucocorticoid or anti-glucocorticoid activity.

Pharmacokinetic studies in animals show a rapid absorption of drospirenone from the gastrointestinal tract and a rapid distribution to the tissue. Metabolism varies considerably between animal species, and is therefore hard to compare with the human metabolism. The cytochrome P450 system does not seem to be involved in the degradation of drospirenone.

A toxicological study involving repeated administration of drospirenone to rats, mice and monkeys found pharmacodynamic effects on the sex organs and interruption of the estrus cycle. Exposure to the combination of ethinylestradiol and drospirenone resulted in an increased weight of the liver and the adrenal gland, and a reduced weight of the ovaries. Combined exposure to drospirenone and ethinylestradiol in a reproduction toxicity study showed a disturbance of the estrus cycle and fetal toxicity. Exposure to drospirenone and ethinylestradiol in the final stage of gestation resulted in effects on the sexual differentiation of male and female fetuses of the rat, but this did not apply to fetuses of the monkey. No proof was found for any mutagenity or carcinogenity of drospirenone, or the combination of drospirenone and ethinylestradiol.

Pharmacodynamics
Phase I ovulation inhibition studies indicated 2 mg as the lower limit for ovulation inhibition. Determination of the optimum dosage of drospirenone in combination with ethinylestradiol, revealed drospirenone 3 mg as the optimum dose as 4 mg drospirenone did not result in further inhibition of ovulation. On the basis of these results, the dosage of 3 mg drospirenone was selected for further investigation.

Phase I studies in men indicated high dosages (15-60 mg) of drospirenone having also anti-mineralocorticoid (anti-aldosterone) properties. The anti-mineralocorticoid effect of drospirenone is due to the competitive inhibition for the binding of aldosterone to the mineralocorticoid receptor. The anticipated clinical effects include an increase in Na^+ excretion and a reduction of the K^+ excretion in the urine. Extensive Phase I studies were performed to investigate the clinical relevance of these anti-mineralocorticoid properties at a much lower dosage of 3-4 mg drospirenone, used for the inhibition of ovulation.

A dose-related increase in plasma renin substrate (angiotensinogen), plasma-renin activity and plasma aldosterone was noted. The effects on angiotensin II and renin were marginal. The urinary excretion of aldosterone metabolites and free aldosterone increased with increasing drospirenone dose. With the exception of an increase in plasma renin substrate (an estrogen-related effect) these effects were not seen during treatment with the reference preparations levonorgestrel and desogestrel.
The Na^+ and K^+ plasma levels remained almost unchanged. During the first treatment cycle, a dose-dependent initial increase in the excretion of Na^+ in the urine up to the second half of the cycle was observed. The excretion reached steady state in the second half of the cycle. During the first treatment cycle, a dose dependent initial reduction in K^+ excretion in the urine occurred, but this remained at a constant level during the second half of the cycle. No marked influence of the ethinylestradiol dose was seen on these effects. After the end of treatment, the values of the RAAS (renin-angiotensin-aldosterone system) returned to their baseline values within a few days. Significant changes in blood pressure, heart rate and body weight were not observed.

Pharmacokinetics
Following oral administration, drospirenone is absorbed rapidly and almost completely. The absolute bioavailability is approximately 85%. Concomitant ingestion of food has a marked effect on the rapidity of the absorption, which may lead to low plasma levels that are clinically significant. The volume of distribution following repeated administration is approximately 4 l/kg and total clearance is estimated at 1.5 ml/min/kg. Drospirenone is more than 95% bound to plasma proteins, though it does not bind to Sex Hormone Binding Globulin (SHBG).

Following repeated administration of 3 mg drospirenone daily, the maximum plasma concentration is about 80 ng/ml ± 20% and the trough concentration is 20 ng/ml ± 40%. The mean elimination half-life of drospirenone as monotherapy or in combination with ethinylestradiol is approximately 30 hours. Steady state is reached after 7 days of administration in each cycle and after each cycle with an accumulation factor of 4.

The pharmacokinetic properties of drospirenone can be described as a dual-compartment model and are linear following dosages of 1 to 4 mg daily. Drospirenone is extensively metabolised. About 20 metabolites were identified. The cytochrome P450 enzyme system is not involved in the formation of the two major metabolites, which did not show any pharmacological activity with regard to the steroid hormone receptors.

The elimination half-life of the metabolites is approximately 57 hours. The pharmacokinetic properties of drospirenone are not influenced by concomitant administration of ethinylestradiol. About 0.6% of the orally administered dose of drospirenone passes into breast milk.

In vivo, drospirenone did not show any inhibition of CYP3A4 or CYP2C19. The pharmacokinetic properties of ethinylestradiol are not influenced by the concomitant administration of drospirenone.

Efficacy
In pharmacodynamic and clinical Phase II studies, the combination of drospirenone 3 mg and 30 microgram of ethinylestradiol provided the best ovulation inhibition and cycle control compared to other dosages. The clinical documentation supporting the indication contraception consisted of 9 Phase II/III studies, of which the two Phase III comparative studies versus Marvelon were considered pivotal. Data of 2,274 women treated with Yasmin were used to analyse the contraceptive action. The study period varied from 6 to 26 cycles, which amounts to a total of 30,110 treatment cycles studied. The total is 29,735 with exclusion of the treatment cycles in which condoms were used. The contraceptive efficacy of Yasmin, with a Pearl Index of 0.57 and an upper limit of the 95% confidence interval of 0.90, is similar to the contraceptive efficacy calculated for the reference product Marvelon. The Pearl Index on the basis of pregnancies that can only be attributed to the method (‘method failure’) was 0.09.

No significant differences were reported between Yasmin and Marvelon as regards the incidence of intermenstrual blood loss, amenorrhea and withdrawal bleeding. The incidence of intermenstrual blood loss decreased with the duration of the treatment, to less than 10%. The incidence of withdrawal bleeding was almost 100%.

The clinical relevance of the anti-mineralocorticoid and anti-androgen properties of the product based on the product's pharmacological profile could not be demonstrated.

Safety
The following most frequent adverse events have been reported during the use of Yasmin: headache, menstrual disorders, painful breasts, nausea, vaginal moniliasis, diarrhoea, depression, leucorrhoea and acne. No marked differences in adverse events were observed between Yasmin and the various reference preparations.
A number of specific safety aspects were evaluated separately. The two most significant contraception studies revealed indirect information about antimineralocorticoid effects.
Routine determinations of the plasma K^+, Na^+ and creatinine levels did not reveal any marked differences between Yasmin and the reference product Marvelon. Clinically relevant effects on vital signs, in particular the blood pressure, have not been observed. Comparative studies with Marvelon with the objective to evaluate the clotting factors and the effects on the lipid and carbohydrate metabolism did not show any marked differences between the two products. The MAH committed to start a large post-marketing safety study, in which, among other things, the incidence of VTE will be followed. Moreover, the MAH committed to carry out an additional haemostasis study after the registration.

Product information
The SPC was drawn up in accordance with recent Dutch and European guidelines for product information and for oral contraceptives. The specific properties of the product, which are similar to those of the progestagen drospirenone, have been sufficiently described.

Benefit/risk assessment
The MEB, on the basis of the data submitted, considered that Yasmin 28, film-coated tablets 3/0.03 mg demonstrated adequate evidence of efficacy for the approved indication as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.
On the basis of the available scientific information, the Board has concluded that the benefit/risk balance is comparable with the reference preparations Marvelon and Microgynon 30. The non-contraceptive effects on acne, lipids and SHBG do not essentially differ from the reference preparation Marvelon. An exception is that the clinical studies indicate that the mild anti-mineralocorticoid properties may result in a mild anti-mineralocorticoid effect.
With regard to safety it can be stated that drospirenone has antagonistic effects on the aldosterone receptor, but in a normal situation this property will not lead to any significant changes in the electrolyte balance. Warnings were included in the SPC text with regard to the concomitant use of medication that influences the electrolyte balance, and patients with severe renal insufficiency or acute renal insufficiency were excluded from treatment.

The other member states mutually recognised the Dutch evaluation for the marketing authorisation in a written procedure.

The Data Lock Points (DLP) for the PSURs are for the first 2 years every 0.5 year. After that the PSUR should be submitted yearly until the results of the post-marketing European active surveillance (EURAS)-study become available. Note: After assessment of the results of the EURAS-study, the PSUR cycle has been changed to 3 yearly (see Annex IV).

The first renewal date is 7 March 2005 (see Annex II).

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

Chemical-Pharmaceutical

- The MAH committed to submit additional experiments to elucidate the lack of mass balance for ethinylestradiol degradation. (see Annex I).

Clinical

- The MAH committed to conduct a comparative haemostasis study with a reference combined oral contraceptive containing levonorgestrel (see Annex III).
- The MAH committed to conduct a post-marketing European active surveillance (EURAS) study (see Annex IV).

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List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
ATE	Arterial thromboembolism
AUC	Area Under the Curve
BP	British Pharmacopoeia
CBG	Corticoid Binding Globulin
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
COC	Combined Oral Contraceptive
CV	Coefficient of Variation
DSG	Desogestrel
DRSP	Drospirenone
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EE	Ethinylestradiol
EMEA	European Medicines Agency
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCP	Health Care Professional
ICH	International Conference of Harmonisation
LNG	Levonorgestrel
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
MRP	Mutual Recognition Procedure
NOHC	Non-oral hormonal contraceptives
OC	Oral contraceptive
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PMS	Premenstrual Syndrome
PSUR	Periodic Safety Update Report
RAAS	Renin-Angiotensin-Aldosterone System
RH	Relative Humidity
SD	Standard Deviation
SHBG	Sex Hormone Binding Globulin
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

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 procedure	Approval/ non approval	Assessment report attached
Post-approval commitment – Mass balance of ethinylestradiol	NL/H/0217/001/MR	post-approval commit-ment	NA	NA	Approved	Y Annex I
First Renewal – 7 March 2005	NL/H/0217/001/R	renewal	22-12-2004	8-7-2005	Approved	Y Annex II
Post-approval commitment – Comparative haemostatis study	NL/H/0217/001/MR	post-approval commit-ment	NA	NA	Approved	Y Annex III
Post-approval commitment – European active surveillance study (EURAS)	NL/H/0217/001/MR	post-approval commit-ment	NA	NA	Approved	Y Annex IV
Type II change to Module 1, 2 and 3. Updated Module 4. Addendum Module 5.	NL/H/0217/001/II/013	II	29-1-2004	30-3-2004	Approved	N
Change in test procedure for active substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance. Other changes to a test procedure, including replacement or addition of a test procedure.	NL/H/0217/001/IB/014	IB	28-6-2004	28-7-2004	Approved	N
Change in the re-test period of the active substance.	NL/H/0217/001/IB/015	IB	28-6-2004	28-7-2004	Approved	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/0217/001/IA/016	IA	12-7-2004	26-7-2004	Approved	N
Change to module 1.	NL/H/0217/001/II/017	II	1-9-2004	10-11-2004	Approved	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. All other manufacturing operations except batch release.	NL/H/0217/001/IB/018	IB	22-10-2004	21-11-2004	Approved	N
Change in batch size of the finished product. Up to 10-fold compared to the original batch size approved at the grant of the marketing authorisation.	NL/H/0217/001/IA/019	IA	22-10-2004	5-11-2004	Approved	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance. From a manufacturer currently approved.	NL/H/0217/001/IA/020	IA	25-5-2005	9-6-2005	Approved	N
Change to module 1, 2 and 5	NL/H/0217/001/II/021	II	21-2-2006	31-8-2006	Approved	N
Change in the specification of an active substance or a starting material/intermediate/reagent used in the manufacturing process of the active substance. Tightening of specification limits.	NL/H/0217/001/IA/022	IA	16-5-2006	30-5-2006	Approved	N
Change in test procedure for active	NL/H/0217/0	IA	16-5-2006	30-5-2006	Approved	N

substance or starting material, intermediate, or reagent used in the manufacturing process of the active substance. Minor change to an approved test procedure.	01/IA/023					
Change in the name and/or address of a manufacturer of the finished product	NL/H/0217/001/IA/024	IA	12-9-2006	26-9-2006	Approved	N
Change in the name and/or address of a manufacturer of the finished product	NL/H/0217/001/IA/025	IA	2-5-2007	16-5-2007	Approved	N
Change in synthesis and the name change of the manufacturer of the drug substance drospirenone	NL/H/0217/001/II/026	II	6-6-2007	17-10-2007	Approved	N
Change in the name and/or address of the marketing authorisation holder in Denmark, Iceland, Norway and Sweden	NL/H/0217/001/IA/027	IA	16-10-2007	30-10-2007	Approved	N
Update of SPC section 4.4 related to venoius thromboembolism (VTE). The results of the EURAS-study will be implemented in the SPC.	NL/H/0217/001/II/028	II	19-7-2007	27-6-2008	Approved	N Please refer to Annex IV
Submission of a revised certificate or suitability (CEP) for the drug substance ethinylestradiol	NL/H/0217/001/IA/029	IA	16-10-2007	30-10-2007	Approved	N
Change in the name and address of the MA-holder in Spain	NL/H/0217/001/IA/030	IA	3-1-2008	17-1-2008	Approved	N
Update of product information (SPC sections 4.2, 4.8 and 5.1 and PIL)	NL/H/0217/001/II/031	II	11-9-2008	7-5-2009	Approved	N
Change in the specification of the finished product. Tightening of specification limits	NL/H/0217/001/IB/032	IB	30-9-2008	21-10-2008	Approved	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/0217/001/IB/033	IB	30-9-2008	21-10-2008	Approved	N
Minor change in the manufacture of the finished product	NL/H/0217/001/IB/034	IB	16-10-2008	5-11-2008	Approved	N
Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier), spacer devices for metered dose inhalers are excluded. Replacement or addition of a supplier.	NL/H/0217/001/IB/035	IB	16-10-2008	5-11-2008	Approved	N
Change (replacement, addition or deletion) in supplier of packaging components or devices (when mentioned in the dossier), spacer devices for metered dose inhalers are excluded. Replacement or addition of a supplier.	NL/H/0217/001/IB/036	IB	16-10-2008	5-11-2008	Approved	N
Addition of new suppliers of the starting material (used for the synthesis of the active substance drospirenone)	NL/H/0217/001/IB/037	IB	16-12-2008	13-1-2009	Approved	N
Change in the specification of the finished product. Tightening of specification limits.	NL/H/0217/001/IB/038	IB	16-7-2009	15-8-2009	Approved	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/0217/001/IB/039	IB	15-7-2009	14-8-2009	Approved	N
Change in the name and/or address of the marketing authorisation holder	NL/H/0217/001/IA/040	IA	1-9-2009	15-9-2009	Approved	N

in France.						

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
Type B.I.a.2	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product	None	20-4-2010	Approval	
Type C.I.4	Change(s) in the Summary of Product Characteristics and Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	SmPC / PL	4-5-2010	Approval	
Type R	Renewal	None	18-6-2010	Approval	
Type C.I.z	Risk Management Plan based on the RMP for Yaz	None	1-11-2010	Approval	
Type B.III.1.a2	Submission of an updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability from an already approved manufacturer for the active substance	None	22-11-2010	Approval	
Type P	Notification for product information amendment under Article 61 (3)	PL	14-1-2011	Approval	
Type PSUR	PSUR submission	None	24-3-2011	Approval	
Type C.I.3.a	Implementation of wording agreed by the competent authority Package Leaflet of human medicinal products intended to implement the outcome of a PSUR,	PL	26-05-2011	Approval	
Type C.I.3.a	Implementation of change(s) requested by the EMEA/Nationai Competent Authority	SmPC / PL	14-6-2011	Approval	
Type A.1	Change in the name and/or address of the marketing authorisation holder	SmPC	04-08-2011	Approval	
Type A.4	Change in the name of the manufacturer of the active substance where no Ph. Eur.Certificate of Suitability is part of the approved dossier from currently Bayer Schering Pharma AG to Bayer Pharma	None	04-08-2011	Approval	
Type A.5a	Change in the name of the manufacturer of the finished product from currently Bayer Schering Pharma AG to Bayer Pharma AG	None	04-08-2011	Approval	
Type A.5b	Change in the name of the manufacturer of the finished product from currently Schering GmbH und Co. Produktions KG to BayerWeimar GmbH und Co. KG	None	04-08-2011	Approval	
Type P	Notification FDA waiver extended	None	6-9-2011	Approval	
Type A.1	Change in the name of the marketing authorisation holder from currently Bayer Schering Pharma AG to Bayer Pharma AG	SmPC	14-10-2011	Approval	
Type A.4	Change in the name of the manufacturer of the active substance where no Ph. Eur.Certificate of Suitability is part of the approved dossier from currently Bayer Schering Pharma AG to Bayer Pharma AG.	None	14-10-2011	Approval	
Type A.5a	Change in the name of the manufacturer of the finished product from currently Bayer Schering Pharma AG to Bayer Pharma AG.	None	14-10-2011	Approval	
Type A.5b	Change in the name of the manufacturer of the finished product from currently Schering GmbH und Co. Produktions KG to Bayer Weimar GmbH und Co. KG	None	14-10-2011	Approval	

Type B.III.1.a2	Submission of an updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability from an already approved manufacturer for the active substance	None	13-4-2012	Approval	
Type B.II.b.1e	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	None	15-05-2012	Approval	
Type B.II.b.2a	Change to importer where batch control/testing takes place, batch release arrangements and quality control testing of the finished product	None	15-05-2012	Approval	
Type C.I.4a	Changes in section 4.8 of the Summary of Product Characteristics with comprehensive update of the ADR table and section 4	SmPC	23-05-2012	Approval	
Type A.7	Deletion of a manufacturing site of the drug product.	None	29-08-2012	Approval	
Type B.III.1.a.1	Submission of a new certificate of suitability from an already approved manufacturer.	None	29-8-2012	Approval	
Type C.I.4 WS	Adapting section 4.4 and 5.1 of the SmPC of all combined oral contraceptives	SmPC	27-11-2012	Approval	
Type C.I.z	Introduction of the Pharmacovigilance System Master File.	None	04-04-2013	Approval	
Type C.I.4 WS	Changes to the SmPc section 4.3 and PIL	SmPC / PL	29-04-2013	Approval	
Type B.II.a.3 b1	Any minor adjustment of the quantitative composition of the finished product with respect to excipients	None	16-05-2014	Approval	
Type B.II.a.3 b6	Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level.	SmPC / PL	16-05-2014	Approval	
Type B.II.b.3 a	Minor change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product.	None	16-05-2014	Approval	
Type B.II.b.4 a	Up to 10-fold change in the batch size (including batch size ranges) of the finished product	None	16-05-2014	Approval	
Type B.II.b.5 b+c	Addition and deletion of in-process tests or limits applied during the manufacture of the finished product.	None	16-05-2014	Approval	
Type B.II.d.1 a	Tightening of specification limits in the specification parameters and/or limits of the finished product.	None	16-05-2014	Approval	
Type C.I.4 WS	Changes in section 4.8 of the SPC to fulfil a commitment related to a PSUR WS	SmPC	25-07-2014	Approval	
Type C.I.1 .a WS	Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure where the medicinal product is covered by the defined scope of the procedure.	SmPC / PL	30-07-2014	Approval	
Type R	Renewal	None	03-02-2015	Approval	
Type C.I.4 WS	Changes refer to the deletion of interaction with antibiotics and update on interactions with HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors	SmPC / PL	17-04-2015	Approval	
Type C.I.4 WS	Update of potential drug interactions in de PI of all COCs.	PL	18-08-2015	Approval	
Type C.I.11.z WS	Other worksharing	None	18-05-2016	Approval	
Type B.III.1.a.2	Submission of an updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability from an already approved manufacturer for the active substance	None	04-08-2016	Approval	
Type B.II.b.3.a	Minor change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product.	None	12-09-2016	Approval	

Type A.5.a	Change in the name and/or address of a manufacturer/importer of the finished product. (including batch release)	None	24-05-2017	Approval	
Type A.5.b	Change in the name and/or address of a manufacturer/importer of the finished product.	None	24-05-2017	Approval	
Type C.I.4	Update SmPC.	SmPC	22-08-2017	Approval	
Type B.III.1.a.2	Submission of an updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability from an already approved manufacturer for the active substance	None	19-09-2017	Approval	
Type C.I.z	Update SmPC.	SmPC	26-02-2019	Approval	
Type C.I.4 WS	Submission of updated ERA report	None	05-11-2020	Approval	
Type B.II.f.1.d	Change in storage conditions of the finished product or the diluted/reconstituted product	SmPC / PL	06-05-2021	Approval	
Type C.I.4 WS	Update SmPC sections 5.3 and 6.6	SmPC	30-06-2021	Approval	

Annex I to the PAR

Post-approval commitment – Mass balance of ethinylestradiol

In July 2001 the MAH submitted additional experiments to elucidate the lack of mass balance for ethinylestradiol (EE) degradation, as committed at the end of the MRP. The MAH focused on the following main points as possible sources for the mass imbalance: formation of gaseous products as EE degradation products (which are hard to quantify once formed), adsorption of EE and/or its degradation products to matrices (e.g. in the product or during analytical testing), the analytical variability in the HPLC method for EE assay and content of degradation products as well as the interference of 100 fold higher dose drospirenone.

Since the lack of mass balance remaining is very minor, there is no need to change the HPLC method used for assay of EE and degradation, nor the specifications for these parameters. Based on the review of the data, the member states considered the post-approval commitment regarding the mass balance of ethinylestradiol for Yasmin 28 film-coated tablets, fulfilled.

Annex II to the PAR

First renewal – 7 March 2005

The first marketing authorisation for Yasmin was granted in the Netherlands on 7 March 2000 and the product was first launched in Germany in November 2000. The duplicate Yira and Yasmin 28 were approved in the Netherlands on 12 April 2000 and 7 April 2000, respectively. The first renewal date was 7 March 2005. This renewal comprises Yasmin, as well as Yira and Yasmin 28.

Update on regulatory authority or manufacturer actions taken for safety reasons

The following table summarises the actions taken by either the regulatory authority or by the MAH. It contains a summary of the most important issues addressed. No relevant actions were taken in the period covered by PSUR1-PSUR3 (7 March 2000 - 6 September 2001).

Period	*Actions*
7 September 2001 – 6 March 2002 (PSUR4)	• VTE risks of Yasmin discussed with the Dutch regulatory authority (MEB) and text of suggested statement is developed. The sentence *It is not known how Yasmin influences the risk of VTE compared to other oral contraceptives* was suggested to be added to Yasmin label. Text was otherwise in line with standard labelling regarding the VTE risks for OCs.
7 March 2002 – 6 March 2003 (PSUR5)	• The Norwegian Medicines Agency (NMA) contacted physicians, nurses and midwives concerning the recent launch of Yasmin and the fact that it was the first OC to contain drospirenone. Four Norwegian VTE reports were mentioned in these communications. It is a common practice for the NMA to follow-up on newly launched products. • Two updates on VTE and ATE reports were submitted to the FDA during the Periodic safety update. • Text suggested to be added in label during PSUR4 regarding VTEs was agreed upon with the MEB.
7 March 2003 – 6 September 2003 (PSUR6)	• EU RMS (MEB, NL) requested that the next PSUR covered a half-year period. The MAH complies with this request. • Based on the cumulative safety analyses the MEB proposed an addition to Yasmin label regarding hepatic events under sections 4.8: *Increased liver enzymes and hepatocellular damage, generally reversible after stopping treatment with Yasmin.* This has not yet been implemented.
7 September 2003 – 6 September 2004 (PSUR7)	• Type II variation: deletion of the sentence *It is not known how Yasmin influences the risk of VTE compared to other oral contraceptives* from Yasmin label and to add that VTE incidence is similar for Yasmin and other COCs (based on EURAS study interim results, see also Annex IV).

5-year Renewal

Risk-benefit assessment

Contraceptive efficacy

Regarding the efficacy of Yasmin, during the total reporting period, 268 reports of unintended pregnancies have been received. The reported breakthrough pregnancies appear to be mainly caused by drug-drug interactions, gastrointestinal disturbances and irregular drug use (missed pills). Taking into account a patient exposure of over 7 million women-years the number of unintended pregnancies is well in line with the Pearl Index calculation on the basis of the pre-registration file.

Safety

Adverse Event(AE)/Adverse Drug Reaction pattern
With a cumulative patient exposure estimate of 91,787,559 cycles (7,060,581 women-years) during the period under review, in total, 2,031 spontaneous reports on adverse drug reactions (ADRs) confirmed by health care professionals (HCPs) were received. Of these HCP reports, 615 cases involved serious ADRs. Most frequently mentioned serious ADRs/AEs were: cholelithiasis, increased liver enzymes, migraine, cerebral venous thrombosis, cerebrovascular accident, pulmonary embolism, and deep vein thrombosis.

Venous thromboembolism
Since 1995, the incidence of venous thromboembolic events is a matter of concern in relation to use of (especially third generation) COCs. Yasmin contains a new type of synthetic progestagen, but a registration file is far too small to reliable assess the incidence of such rare adverse events like venous thromboembolism. During the registration procedure of Yasmin the MAH therefore formally committed to conduct an active postmarketing surveillance study comparing the safety profile of three different groups of COCs: COCs containing drospirenone (Yasmin), COCs containing levenorgestel, and OCs containing other progestagens (EURAS study, Annex IV). Additionally, a commitment was included to conduct a comparative haemostasis study (Annex III) versus the LNG-COC Microgynon.
Apart from the EURAS-study and the haemostasis-study, the MAH also performed a postmarketing study at the request of the FDA, i.e. INGENIX-study, which was based on an USA insurance database. The final results of the EURAS-, haemostasis- and INGENIX-studies were not yet available at the time of the renewal.

The interim results of the ***EURAS study*** so far did not indicate a particular concern for Yasmin. Despite a higher baseline risk profile in users of Yasmin (higher BMI) compared to users of other OCs, the incidence for both venous and arterial thromboembolic events was similar in all three cohorts. In conclusion, based on the interim data available, there is no signal that Yasmin users have an increased risk for VTEs compared to users of second generation COCs (levonorgestrel—containing COCs) and to users of “other COCs” (mainly desogestrel-, dienogest- or chlormadinonacetate-containing COCs).

Additionally, one other post-marketing study concerning VTE risk and Yasmin use was ongoing:
The ***Ingenix study*** (US) is a prospective cohort study based on claims data from a major health care provider (J.D. Seeger et al, 2007, Obstet. Gynecol., 110(3):587-93). Based on preliminary claims, the rate for possible VTE/ATE was similar between Yasmin and other OC users.

Overall, post-marketing experience presented a safety profile similar to that known from other combined oral contraceptives. So far, interim-data on the relative risk of venous thrombo-embolism do not indicate an increased risk in Yasmin users compared to users of other COCs.

In conclusion, the benefit/risk ratio for Yasmin in the approved indication remains positive and renewal can be granted.

Overall conclusion

The risk-benefit assessment for Yasmin remained unchanged over 5 years. Thus, renewal of the marketing authorisation was granted by the concerned member states with a new renewal date of 7 March 2010. Until finalisation of the EURAS-study PSURs should be submitted yearly.

Annex III to the PAR

Post-approval commitment – Comparative haemostasis study

Introduction

During the MRP procedure, the MAH committed to conduct a comparative haemostasis study with a reference combined oral contraceptive (COC) containing levonorgestrel. It was agreed with the MEB and concerned member states that the choice of haemostatic parameters should depend on the outcome of the scientific discussion on the so-called 3rd generation COCs at the EMEA and the identification of haemostatic parameters, which are predictive for the thrombosis risk of COC users. The haemostasis study is a single-center, double-blind, randomized, crossover study to investigate the impact of the oral contraceptive Yasmin (30 μg EE/3 mg DRSP) compared to Microgynon (30 μg EE/150 μg LNG) on haemostasis parameters in 40 healthy female volunteers over 2 periods of 7 treatment cycles.

Background

Use of COCs is associated with a higher risk for VTEs compared to non-users. During the MRP procedure, it was discussed whether there is a need for more information on effects of Yasmin on haemostasis, although at that time no established surrogate variable for the clinical endpoint of VTE was available. Despite that, some concerned member states considered that an additional haemostasis study was needed investigating those variables that might be of interest in the quest for a suitable surrogate parameter for VTE. In July 2005 the CHMP "Guideline on clinical investigation of steroid contraceptives in women" was revised. According to this revised Guideline, biological variables that may be related to VTE risk, should be investigated for a new combined (oestrogen-progestogen) contraceptive product. Variables suggesting such different pharmacological effects may include prothrombin fragment 1+2, APC resistance (ETP-based, APTT-based), d-dimer, factor VII, factor VIII, factor II, antithrombin, protein S, protein C and SHBG. As comparator, levonorgestrel + ethinylestradiol (150/30μg) where VTE risk has been established in observational studies, was considered appropriate. The protocol of this study was submitted to the MEB and to the concerned member states in February 2001 and was discussed and approved in the PhVWP in November 2002. Additionally, the exploratory ETP-based APC resistance test and study protocol was further reviewed by scientists involved in the development of this test.

Design and sample size

The study was a single-center, double-blind, randomized, cross-over study performed in Germany. A total of 40 healthy women were to be enrolled, and randomly assigned to 1 or 2 treatment sequences, i.e. 20 women per treatment group. Each subject was to be treated for 2 periods of 7 cycles with either Yasmin or Microgynon 30. The 1st treatment period (which lasted 6.5 months) was followed by a washout phase of 3 cycles. After the washout phase, the 2nd treatment was given for another 7 cycles (or 6.5 months).

The inclusion criteria were:

1. Healthy subjects requesting contraception between 18 and 35 years
2. Smokers could also be included provided that the women were not older than 30 years of age at study inclusion
3. Non-suspicious Pap-smear taken on visit 1, or available report of smear taken within the last 6 months before inclusion in the study

The exlusion criteria were:

1. Presence or history of thromboembolic process in veins or arteries, or a known genetic component, VTE in a close relative at a younger age (≤ 40 years)

2. Blood pressure consistently ≥ 140 mm Hg systolic and / or ≥ 90 mm Hg diastolic, hypertension, diabetes mellitus, severe dyslipoproteinemia, severe liver dysfunction or disease, kidney disease with impaired renal function, pancreatitis, acute visual disturbances, migraine.
3. Obesity, i.e. body mass index (BMI) > 30 kg/m2
4. Other diseases: endometriosis, pemphigoid gestationis during pregnancy, endometrial hyperplasia, genital bleeding of unknown origin or uterus myomatosus
5. Use of sex hormones within 3 cycles, or intramuscular administration (depot) within 6 months prior to start of study treatment.

Selection of haemostatic variables:
The variables selected were divided into primary haemostasis variables, which are considered established as predictive for VTE risk and secondary variables that are exploratory, i.e. no proven predictive value for VTE risk is supported. Blood samples were drawn for assessment of haemostasis parameters at baseline, end of period 1 (cycle 7), during washout (cycle 10), and at the end of period 2 (cycle 17), between days 15-21 of the cycle.

Primary haemostasis variables:
Absolute changes from corresponding baseline values during treatment of:

Factor VIII (activity):	coagulant factor, favors clotting when increased
Fibrinogen:	coagulant factor, favors clotting when increased
Protein C activity:	anticoagulant factor, favors clotting when decreased
Antithrombin III activity:	anticoagulant factor, favors clotting when decreased
APTT-based APC resistance ratio:	when decreased, the sensitivity to activated protein C is reduced, which favors clotting

Secondary haemostasis variables:
Absolute changes from corresponding baseline values during treatment of:

Factor VII (activity):	procoagulant factor, favors clotting when increased
Protein S (activity):	anticoagulant factor, favors clotting when decreased
Prothrombin fragments 1+2:	indicates increased thrombin formation when increased (thrombin turn-over↑)
D-dimer:	indicates increased fibrinolysis when increased (fibrin turn-over↑)
ETP-based APC resistance ratio (Rosing):	when increased, the sensitivity to activated protein C (APC) is reduced, which favors clotting

Results

Primary haemostasis variables
Absolute changes and analysis of variance (ANOVA) were calculated for the primary haemostasis variables.

- Factor VIII activity and fibrinogen (procoagulants) increased for both Yasmin and Microgynon, with no significant treatment difference.
- Antithrombin III activity (anticoagulant) was largely unchanged, also without significant difference between Yasmin and Microgynon.
- Protein C activity (anticoagulant) increased, significantly more for Yasmin (p = 0.0068 for FAS) than for Microgynon.

- APC resistance ratios showed a small decrease, significantly more for Yasmin (p = 0.0001 for FAS) than for Microgynon.

No statistically significant sequence or period effects were found for any of the primary haemostasis variables. The number of subjects that actually had outcomes outside the reference range is low, and there is little difference in the number of subjects in whom final values were outside the reference ranges between groups.

Secondary haemostasis variables
For the exploratory secondary haemostasis variables, absolute changes were calculated. No statistical analysis by ANOVA was performed.

- Factor VII activity (procoagulant) increased more for Yasmin than for Microgynon.
- Protein S activity (anticoagulant) showed an increase for Microgynon and a decrease for Yasmin.
- Prothrombin fragments 1+2 (marker of fibrinolysis) increased comparably for both treatments.
- D-dimer levels (marker of fibrinolysis) also increased for both Yasmin and Microgynon, with very large standard deviations and no treatment difference.
- APC resistance (=sensitivity) ratio levels (Rosing test) were measured in 2 separate laboratories due to the lack of validation of this experimental assay. There were large differences in individual values at comparable time points between the laboratories. Values increased for both treatments, and more for Yasmin than for Microgynon. Regarding the APC sensitivity ratio, there is no validated reference range for women for this exploratory test.

There is little difference in the number of subjects in whom final values were outside the reference ranges between groups.

Overall conclusion

This study was the first that has been performed as a postregistration commitment to specifically investigate haemostatic variables other than the standard set so far used in clinical trials to investigate effects on haemostasis of a COC. From January 2006 on, for all **new** combination contraceptives, biological variables that may possibly be related to VTE risk, should be investigated according to the "Guideline on clinical investigation of steroid contraceptives in women". The double-blind randomised cross-over study design is in full agreement with current recommendations. The primary haemostatic variables selected are accepted as being probably predictive for VTE risk, as substantial changes (deficiencies) in these parameters in an individual subject could indicate a higher individual risk of developing a VTE. The secondary variables selected are still exploratory. The set of variables tested largely covers those recommended by the EMEA.

Conclusion on haemostatic factors
The effects observed for primary haemostasis variables selected were comparable in both treatment groups, but more pronounced during Yasmin with regard to factor VIII, fibrinogen and protein C activity.

With regard to the secondary variables selected, the procoagulant variable Factor VII has increased in both treatment groups. Additionally, the increases in prothrombin fragments 1+2 and D-dimer, indicate an increase in fibrinolysis, compatible with the assumption that an increase in pro- and anticoagulant factors will lead to a higher fibrin turn-over. However, it should be taken into account that the level of D-dimer is a very non-specific variable.
The effects observed on secondary variables selected were comparable in both groups, with the exception of anticoagulant protein S activity, which slightly decreased during Yasmin use but slightly increased during Microgynon 30. A decrease in protein S activity during COC use is reported in public literature, but the test results are considered difficult to interpret. The only variable selected in this study that resulted in an increase outside the reference ranges with both COCs, seemingly more for Yasmin

than for Microgynon 30, appeared the ETP-based APC resistance ratio according to Rosing et al. Several publications have promoted this particular test as the most promising variable in the quest for suitable surrogate parameter for VTE risk. However, adequate interpretation of these results is still not possible, as the test is not validated in relation to the clinical end point of VTE.

In conclusion, the results of the haemostasis study suggest the effects of Yasmin use on the haemostatic balance to be more pronounced than during Microgynon 30, the COC that is considered to have lowest risk on VTE (second generation COC). As unfortunately up to now none of the haemostatic variables selected in this study or any other known variable can be pointed out as a generally accepted surrogate parameter for VTE in women with normal baseline risk for VTE, it is not considered justified to conclude that the differences found will translate into a higher risk for VTE in healthy women.
Moreover, results of any surrogate parameter should never overrule data on the clinical endpoint, in this case the clinical endpoint of VTE. In the situation of Yasmin, as part of a postapproval commitment a large postmarketing study is being performed, i.e. the EURAS study (see Annex IV), that compares the occurrence of rare clinical endpoints, such as VTE, among users of Yasmin, users of LNG-containing COCs (second generation COCs), and users of other COC (mainly third generation COCs) in more than 55.000 women in 7 European countries. In the EURAS-study no increased risk of VTE and ATE was noted in users of Yasmin, as compared to users of LNG-OCs, and users of other-OCs (mainly 3rd generation OCs).

Based on the review of the data of the haemostasis study, the member states considered the post-approval commitment for Yasmin 28 film-coated tablets, fulfilled.

Annex IV to the PAR

Post-approval commitment – European Active Surveillance (EURAS) study

Introduction
During the MRP, the MAH committed to conduct an active post-marketing surveillance study. The EURAS study was a prospective, controlled, non-interventional, active surveillance cohort study primarily designed to characterize and compare the risks of short- and long-term use of oral contraceptives in three different cohorts (i.e. Yasmin, levonorgestrel (LNG), and Other OC cohort) (J.C. Dinger et al, 2007, Contraception, 75(5):344-54). The protocol of this study was submitted to the MEB and to the concerned member states in February/March 2001, and was discussed and approved by the PhVWP in December 2002.

Design and sample size
The primary objective was to compare the incidence of cardiovascular events in Yasmin users, in particular venous thromboembolism (VTE) and arterial thromboembolism (ATE), to the incidence in LNG-containing OC-users and all other-OCs (mainly desogestrel and gestodene (3rd generation) COCs) users. LNG-OCs are considered to have the lowest impact on VTE risk, whereas the Other OCs have the highest impact. The comparator-arms are considered well-chosen as the VTE risk of the comparator is relatively low. As the VTE risk of the Other OCs cohort is higher, the relative position for VTE risk of Yasmin between these 2 comparators can be evaluated.
Non-inferiority was opted for. Sample size calculations indicated that 50,000 patients with a total OC exposure of at least 100,000 WY should be sufficient to reach this goal. The upper limit of the risk ratio (drospirenone/levonorgestrel) should not exceed 2. For LNG-OC the lowest VTE risk has been reported, therefore this non-inferiority margin was accepted.
Additionally, the MAH took the advantage to collect data of those women, who switched to non-oral hormonal contraception (NOHC) and those who stopped hormonal contraception all together (no-use cohort).

Recruitment and participants
Women from seven European countries participated: Austria, Belgium, Denmark, France, Germany, the Netherlands, and the United Kingdom. The study participants were women who were new OC users, i.e. first-ever users (so-called starters) or OC switchers of three different groups of OCs: OCs containing drospirenone (Yasmin), OCs containing LNG, OCs containing other progestagens (desogestrel, dienogest, chlormadinonacetate were most frequently used). No other specific inclusion or exclusion criteria were made because of the non-interference approach of the study design. Assessments for each participating woman were scheduled every 6 months, by means of questionnaires in which information on adverse events could be included.
Overall, 59,510 women were enrolled into the study and followed up for a period of up to 5 years. The large study size, 112,659 women-years of observation, on which these estimates are based, and the very low drop-out rate (2.4%) allow that conclusions can be drawn on the occurrence of rare serious adverse events like VTE and ATE.

Validation of cases
The patient-reported events were classified in confirmed and non-confirmed cases by three independent medical experts. The reported VTE was classified as confirmed if at least one adjudicator had classified the event as confirmed before the discussion of split decisions took place. This blinded adjudication process is thorough and is expected to result in the inclusion of adequately confirmed VTE occurrences. In addition, it allows for the inclusion of cases even if only one adjudicator has classified the event as confirmed. The method applied for the validation of VTE cases by blinded adjudication was considered adequate by the MEB.

Enrolment of OC user cohorts
Three data sets were analysed separately: Intention to treat dataset (ITT), "As Treated" dataset (AT) and Per Protocol data set (PP). AT and PP analyses only differed by 371 women who were included with NOHC. No relevant differences were observed between the two datasets. The point estimates of the risks for VTE and ATE in the ITT, AT and PP data sets were similar.

Overall, about 23% of the subjects switched to another hormonal contraceptive and about 45% of the subjects stopped hormonal contraception either temporarily or permanently. Therefore, the same subject may contribute women years to more than one study arm (Table II.1).

Table IV.1: Number of women enrolled, excluded, analysed and women years of observation/use.

Women	Number
Enrolled	59,510
Excluded[A]	836
Analysed	58,674
Women years of observation[B]	
Overall	142,475 WY
Yasmin	28,621 WY
LNG	31,415 WY
Other OC	52,623 WY
NOHC	4,049 WY
Non-users	25,767 WY

[A] Women who 1) refused to sign informed consent, 2) were enrolled two or more times by one or more study centers, 3) continued their old OC (long-term user), or 4) did not use any OC.
[B] A switcher during the observation period contributed women years to more than one study arm. Non-users-women-years refers to switchers, who stopped using hormonal anti-conception for a period of time during the follow-up.

Comparison of the baseline risks among user cohorts
At baseline, no major differences between the OC user groups were found for most of the risk factors examined. Regarding the established risk factors for VTE, a higher BMI was noticed in the Yasmin group [(17.99% (Yasmin) vs 14.64 (LNG cohort) and 12.58 (other OC cohort)].

Additional analyses on starters and switchers
It is known from the scientific literature that OCs increase VTE maximally during the first year of use, after which the risk declines (so-called starter effect). It is also known that women at high risk tend to switch selectively to the most recently marketed products (so-called switcher effect). Among the three OC cohorts approx. 20% of the study participants were starters (Yasmin 19.0, LNG 22.9, Other OCs 20.1, NOHC 12.4) and approx. 80% were switchers (Yasmin 81.0, LNG 77.1, Other OCs 79.9, NOHC 87.6).

VTE results
A total of 103 VTEs were observed in the OC-cohorts, and 118 VTE events were observed in all cohorts analysed (Table II.2).
The estimated incidence rates per 10.000 women years were comparable between the OC-cohorts; Yasmin (DRSP) cohort: 26 events (9.1 events/10.000 WY; 95% CI: 5.9 – 13.3), LNG cohort: 25 events (8.0 events/10.000 WY; 95% CI: 5.2 – 11.7) and Other OCs cohort: 52 events (9.9 events/10.000 WY; 95% CI: 7.4 – 13.0).
The relative VTE risk of Yasmin versus LNG-OCs is 1.14 (0.66-1.97), and 0.92 (0.55-1.50) versus Other OCs, indicating that non-inferiority has been proven. The incidences estimated in the three treatment groups appeared to be considerably higher than anticipated in the assumptions on non-inferiority. However, the upper limit of the risk ratio is still below 2.

In the validation process for self-reported VTE, 17 events were considered potential i.e. doubtful (4 in Yasmin, 4 in LNG-OCs, and 6 in the Other-OC cohort). The inclusion of these potential VTEs with confirmed VTEs does not lead to any modification of the results regarding VTE risk for Yasmin.

Table IV.2: Thromboembolic events: Number, incidence and 95% confidence intervals per cohort (AT analysis)

Category	Yasmin (28,621 WY)		LNG (31,415 WY)		Other OCs (52,623 WY)		NOHC (4,049 WY)		No use (25,767 WY)		Total
	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	Nos.	Incidence* & 95% CI	Nos.
All TE	28	9.8 (6.5-14.1)	34	10.8 (7.5-15.1)	61	11.6 (8.9-14.9)	5	12.3 (4.0-28.8)	15	5.8 (3.3-9.6)	143
of which Fatal	0	0.0 (0.0-1.3)	3	1.0 (0.2-2.8)	0	0.0 (0.0-0.7)	0	0.0 (0.0-9.1)	0	0.0 (0.0-1.4)	3
All VTE	26	9.1 (5.9-13.3)	25	8.0 (5.2-11.7)	52	9.9 (7.4-13.0)	3	7.4 (1.5-21.6)	12	4.7 (2.4-8.1)	118
of which PE	7	2.4 (1.0-5.0)	7	2.2 (0.9-4.6)	11	2.1 (1.0-3.7)	1	2.5 (0.1-13.8)	0	0.0 (0.0-1.4)	26
VST	0	0.0 (0.0-1.3)	0	0.0 (0.0-1.2)	3	0.6 (0.1-1.7)	0	0.0 (0.0-9.1)	1	0.4 (0.0-2.2)	4
All ATE	2	0.7 (0.1-2.5)	9	2.9 (1.3-5.4)	9	1.7 (0.8-3.2)	2	4.9 (0.6-17.8)	3	1.2 (0.2-3.4)	25
of which AMI	0	0.0 (0.0-1.3)	5	1.6 (0.5-3.7)	4	0.8 (0.2-1.9)	0	0.0 (0.0-9.1)	2	0.8 (0.1-2.8)	11
CVA	2	0.7 (0.1-2.5)	3	1.0 (0.2-2.8)	5	1.0 (0.3-2.2)	2	4.9 (0.6-17.8)	1	0.4 (0.0-2.2)	13

* Incidence is given in events per 10^4 WY

ATE results

A total of 20 ATE (mainly AMI and stroke) were observed in the OC-cohorts.

The estimated incidence rates per 10.000 women years were comparable between the OC-cohorts; Yasmin cohort: 2 events (0.7 events/10.000 WY; 95% CI: 0.1 – 2.5), LNG cohort: 9 events (2.9 events/10.000 WY; 95% CI: 1.3 –5.4) and Other OCs cohort: 9 events (1.7 events/10.000 WY; 95% CI: 0.8 – 3.2).

Additional risk factors for VTE

No other risk factors than OC-use were identified in 1/26 (Yasmin cohort), 2/25 (LNG-cohort), and 6/52 (Other OC cohort) VTE cases (8.7% of cases). An overview of additional VTE risk factors is summarized in Table II.3.

Table IV.3: Overview of additional VTE risk factors present at time of VTE

	n VTE	Age 35+	BMI 25+	Fam. history	Pers. history	Genetic factors	Immob. Surgery, trauma	Long flight/ travel	Pregn. Delivery	Cancer
Yasmin	26	7 (27%)	12 (46%)	12 (46%)	3 (12%)	9 (35%)	5 (20%)	1 (4%)	1 (4%)	0
LNG	25	10 (40%)	10 (40%)	11 (44%)	1 (4%)	3 (12%)	8 (32%)	1 (4%)	0	1 (4%)
Other	52	21 (40%)	17 (33%)	12 (23%)	4 (8%)	11 (21%)	13 (25%)	2 (4%)	0	2 (4%)
Total	103	38 (37%)	39 (38%)	35 (34%)	8 (8%)	23 (23%)	26 (25%)	4 (4%)	1 (1%)	3 (3%)

Note: As almost 60% of women with VTE had more than 1 additional risk factor, the total percentage exceeds 100%.

Cox regression analysis
A Cox regression analysis was carried out in the AT treated data set.
For VTE, the following pre-defined confounder variables were included in the Cox regression model: **age, BMI, duration of use, and VTE history**. The adjusted hazard ratio for Yasmin vs. LNG was 1.05 (95 % CI: 0.61-1.81), whereas the unadjusted hazard ratio was 1.14 (95% CI: 0.66 – 1.97).
For ATE, Cox regression analysis was carried out including pre-defined confounder variables of **age, BMI, smoking, and hypertension**. The adjusted hazard ratio for Yasmin vs. LNG-OCs was 0.25 (0.05 – 1.17). These hazard ratios are accepted, since in the worst case scenario (upper limit of 1.81) an increased risk greater than 2 can be exluded. In conclusion, none of the potential confounders selected had a relevant impact on the hazard ratios for the comparison among cohorts.

Subgroup analyses
Subgroup analyses in *switchers and starters* were performed. Only 13 VTE occurred in starters (Yasmin cohort: 0, LNG cohort: 2, Other OCs cohort: 7, NOHC cohort: 1, no use: 3). This number is too small for a meaningful analysis of starters. An additional multivariate analysis including the variable switcher/starter did not change the hazard ratio estimate for VTE for Yasmin versus the LNG-containing OCs and Other OCs cohort.

Another subgroup analysis was carried out versus *monophasic LNG-OCs containing 30 μg ethinylestradiol*. By using a subgroup of users of monophasic LNG-OCs only as comparator, the triphasic LNG-OCs which are reported to have a higher increased VTE risk than monophasic LNG-OCs were excluded. A total of 17 VTEs were observed in the LNG/30μg ethinylestradiol sub-cohort and 26 VTEs in the Yasmin cohort. This corresponds to an incidence of $10.2/10^4$ WY for the LNG sub-cohort and $9.1/10^4$ WY for the Yasmin cohort. The Cox regression analysis yielded a crude hazard ratio for Yasmin of 0.89 (95% CI: 0.48 – 1.63) and an adjusted hazard ratio of 0.82 (95% CI: 0.45 – 1.51). In conclusion, excluding triphasic LNG-OCs did not alter the results.

Overall conclusion
The results of the other postregistration commitment, the Yasmin haemostasis study (see Annex III) suggested that the effects of Yasmin use on the haemostatic balance were more pronounced than during Microgynon 30 (second generation COC) use. In view of the results of the EURAS study it is concluded that these more pronounced effects on haemostasis did not translate in a clinically relevant higher increase in risk of VTE during Yasmin use.

The observed incidence rates of the EURAS study in all three cohorts are 2-fold higher than noted in retrospective epidemiological studies (incidence rates of 2 to 4 cases per 10.000 women years). A similar pattern is noted for ATEs. In general, results from prospective cohort studies have more weight than retrospective cohort studies. This difference is considered due to the different inclusion cirteria. The retrospective cohorts only analysed those women with no additional risk for VTE. In the EURAS study no other specific inclusion or exclusion criteria were made, because of the non-interference approach of the study design. Therefore, also women with risk factors for VTE had been included.

No increased risk of VTE and ATE was noted in users of Yasmin, as compared to users of LNG-OCs, and users of Other-OCs (mainly 3rd generation OCs). Based on the review of the data of the post-marketing European active surveillance study (EURAS) study, the member states considered the post-approval commitment for Yasmin 28 film-coated tablets, fulfilled.

After assessment of the results of the EURAS study, the PSUR cycle has been changed to 3 yearly.

A type II variation has been started to implement the data of the EURAS-study in the SPC (NL/H/0217/001/II/028). This variation has been approved on 27 June 2008.

ANNEX V – 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,	$DT_{50\ water}$ = 8.5/25/11 d (r/l/l)	r=river; l=lake

	aerobic	$DT_{50, system}$ = 51/76/59 d (r/l/l)			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.