Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for levonorgestrel / ethinyloestradiol

Proprietary Product Name: Seasonique

Sponsor: Teva Pharma Australia Pty Ltd

December 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
ATE	arterial thromboembolic event
AUC	area under the plasma drug concentration-time curve
AUC_{t1-t2}	area under the plasma drug concentration-time curve from t1 to t2
BMD	bone mineral density
CHC	combined hormonal contraceptive
CHMP	Committee for Medicinal Products for Human Use
Cmax	maximum serum concentration of drug
CMI	Consumer Medicine Information
COC	combined oral contraceptive
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
HFI	hormone free interval
OCP	oral contraceptive formulation
PD	pharmacodynamic(s)
PI	Product Information
PK	pharmacokinetic(s)
RMP	Risk Management Plan
SAE	serious adverse event
t½	elimination half life
Tmax	Time taken to reach the maximum concentration (Cmax)
VTE	venous thromboembolic event

I. Introduction to product submission

Submission details

Type of submission:	Major variation (change in dosage amount and regimen)
Decision:	Approved
Date of decision:	23 May 2016
Date of entry onto ARTG	24 May 2016
Active ingredients:	Levonorgestrel/ethinyloestradiol
Product name:	Seasonique
Sponsor's name and address:	Teva Pharma Australia Pty Ltd Level 2, 37 Epping Road Macquarie Park NSW 2113
Dose form:	Film coated immediate release tablet in combination pack
Strengths:	150 µg (levonorgestrel)/30 µg (ethinyloestradiol) tablet and 10 µg (ethinyloestradiol) tablet
Container:	The tablets are packaged in PVC/TE/PVDC//AL blisters. The product is a composite pack consisting of 84 x levonorgestrel (150 µg)/ethinyloestradiol (30 µg) film coated immediate release combination tablets and 7 x ethinyloestradiol (10 µg) film coated immediate release tablets. Each pack provides for a 91 day regimen.
Pack size:	Each pack provides for a 91 day regimen (84 combination tablets + 7 mono tablets).
Approved therapeutic use:	Seasonique is indicated for use as an oral contraceptive.
Route of administration:	Oral
Dosage:	The dosing regimen commences with the first combination tablet from 'Month 1' blister on the first day of the menstrual bleed or (if changing from another combined hormonal contraceptive drug (COC)) on the day after the last active tablet of their previous COC. The recommended dose is one pink combination tablet daily for 84 consecutive days followed by one white (10 µg) ethinyloestradiol tablet once daily for 7 days.
ARTG number:	238384

Product background

This AusPAR describes the application by Teva Pharma Australia Pty Ltd to register a new product (trade name: Seasonique) with a major variation comprising of a change in dosage amount and dosage regimen.

Although this is a new product, the submission is described as major variation, which covers changes in dosage amount, frequency of use or dosage regimen - as its constituent substances ethinyloestradiol and levonorgestrel are already used together in a number of combined oral contraceptive (COC) formulations currently approved for use in Australia. Altogether there are 21 COCs so registered. All of these are designed for use in a 28 day cycle regimen, imitating the normal human menstrual cycle. The majority employ ethinyloestradiol and levonorgestrel at a dosage of either 30 µg/150 µg or 20 µg/100 µg for 21 days followed by a 7 day hormone free interval (HFI) achieved by either placebo tablets or missed dosage. One preparation uses a dose ratio of 50 µg/125 µg. Three others employ a triphasic dosage regimen of 30 µg ethinyloestradiol and 50 µg levonorgestrel for 6 days, followed by 5 days of 40 mg/75 µg and then 10 days of 30 mg/125 µg, followed by 7 placebo tablets.

Ethinyloestradiol and levonorgestrel are synthetic steroid hormones with predominantly oestrogenic and progestogenic actions, respectively.

The proposed indication for Seasonique is:

> *for use as an oral contraceptive.*

The novel aspect of this product with regard to registration in Australia is the use of an extended cycle regimen for this particular combination of synthetic sex steroids. The principle of the extended cycle regimen is not novel, as it is described in the literature,[1] and a 91 day cycle product similar to Seasonique but including a 7 day HFI rather than 7 days of ethinyloestradiol 10 µg (Seasonale) has been registered in the US since 2003 and in Canada since 2007. Also, a formulation containing a different combination of synthetic steroids (ethinyloestradiol 20 µg and drospirenone 3 mg) in a 120 day cycle has been registered in Australia since 2012.

Regulatory status

Seasonique is registered in the US (approved 25 May 2006), Canada (approved 30 March 2010), and in various EU countries via the decentralised procedure (European Commission decision 12 January 2015).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

[1] Edelman A. Menstrual nirvana: amenorrhoea through the use of continuous oral contraceptives. *Curr Womens Health Rep.* 2: 434 (2002).

II. Quality findings

Introduction

The product is to be supplied in three monthly blisters packaged inside an inner carton folder which is placed within an aluminium foil pouch and sealed, then packaged in an outer carton. Each inner carton contains 2 blisters containing 28 combination tablets and 1 blister containing 28 combination tablets + 7 ethinyloestradiol 10 µg tablets. Each blister is labelled by month (Month 1 and Month 2 for combination tablet blisters and Month 3 for the blister containing combination + mono tablets).

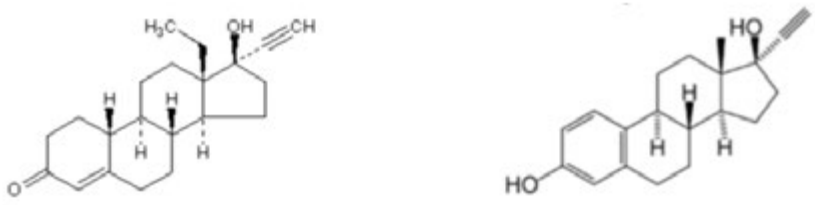
The product is indicated for use as an oral contraceptive. The dosing regimen commences with the first combination tablet from Month 1 blister on the first day of the menstrual bleed or (if changing from another COC) on the day after the last active tablet of their previous COC. The recommended dose is one pink combination tablet daily for 84 consecutive days followed by one white (10 µg) ethinyloestradiol tablet once daily for 7 days.

Both active ingredients are subject to British, European and US Pharmacopoeia drug substance monographs.

Drug substance (active ingredient)

Levonorgestrel and ethinyloestradiol drug substances (Figure 1) are each subject to an European Directorate for the Quality of Medicines (EDQM) Certificates of Suitability.

Figure 1: Chemical structures of levonorgestrel and ethinyloestradiol.



Levonorgestrel Ethinyloestradiol

One polymorphic form is known for anhydrous ethinylestradiol, while the manufacturing process for levonorgestrel yields a single crystalline form of the drug substance. Both levonorgestrel and ethinyloestradiol drug substances are micronised prior to use in the product to the acceptable particle size distribution (PSD) specification limits. The manufacturing and quality control of the drug substances (including the drug substance specifications) are acceptable.

Drug product

The product is manufactured by conventional dry blending and compression manufacturing and film coating process.

The levonorgestrel/ethinyloestradiol tablet contains 150 µg levonorgestrel, 30 µg ethinyloestradiol as the active ingredients and 5 other conventional and commercially sourced excipients including anhydrous lactose, hypromellose, microcrystalline cellulose, magnesium stearate and the proprietary coating agent Opadry Pink YS-1-14012. The ethinyloestradiol monotherapy tablet contains 10 µg ethinyloestradiol and 5 other conventional and commercially sourced excipients including anhydrous lactose, polacrillin

potassium, microcrystalline cellulose, magnesium stearate and the proprietary coating agent Opadry II White Y-22-7719.

The quality of the product is controlled by specifications that includes tests and limits for Appearance, Identification, Assay, Uniformity of Dosage Units, Related Substances, Dissolution, Water Content and Microbiological Quality.

While the dissolution test method is acceptable, the dissolution acceptance limit was not adequately justified by the data obtained from clinical batches. Although the sponsor agrees that the limits that are supported by the clinical batch data would provide a more discriminatory method and better product quality control, the sponsor has asked to retain the originally proposed (wider) limit. If the sponsor does not amend the dissolution specification limits in the response, then the Pharmaceutical Chemistry Section (PCS) of TGA recommend that the supported dissolution limits will be made a condition of registration. This matter remains outstanding, pending the sponsor's response to the evaluation report.

The proposed release and expiry limits for specified degradation products are in line with the International Conference on Harmonisation (ICH) identification and qualification threshold of 1.0%, based on the recommended daily dose of 150 µg levonorgestrel and 30 µg ethinyloestradiol (as the worst case between the combination versus mono tablets). However, the storage stability data showed an increasing trend in impurities Δ9,11–Ethinylestradiol, 6-Keto-ethinylestradiol, and single unknown impurity for the combination tablet. However, the release and expiry related substance specification limits do not permit such increase and therefore, the release limits are not acceptable and no shelf life can be set at this stage. The same applies to the mono tablet, where the storage stability data showed an increasing trend in Δ9,11–Ethinylestradiol and 6-Keto-ethinylestradiol, but again the release and expiry specification limits do not permit such increases. For this reason, PCS cannot recommend approval.

All other release specification limits and expiry specification limits are otherwise acceptable.

The analytical methods used to analyse the product were adequately described and validated.

Acceptable Good Manufacturing Practice (GMP) clearance was provided for most of the manufacturing sites, except for the finished product manufacturer. The sponsor has submitted an application to renew the GMP clearance for this site, but a new GMP clearance has not been issued. This matter remains outstanding.[2]

The stability data supplied supported a **shelf life of 24 months** for the unopened product in PVC/TE (thermo-elastomer)/PVDC//AL blisters when it is **stored below 25 °C** (in the original pack to protect from light and moisture).

Update

Acceptable GMP clearance was subsequently provided for this manufacturing site.

The sponsor subsequently agreed to change the dissolution specification limits and related substances release specification limits. The dissolution test method is acceptable. The dissolution acceptance limits are supported by the clinical batch dissolution data and are acceptable.

The revised release specification limits for related substances are acceptable on the basis of the stability trends.

[2] See update on dissolution specification limits and related substances release specification limits below.

Biopharmaceutics

The pivotal clinical studies were performed using Seasonique CT which is a different formulation to the proposed product with respect to the coating agents and colours. To justify this approach, the sponsor provided adequate physico-chemical data (including dissolution profile data) and it is accepted from a pharmaceutical chemistry perspective that the proposed tablets will be bioequivalent to the clinical trial tablets.

Quality summary and conclusions

There are no further outstanding issues that require resolution and approval can be recommended from a pharmaceutical chemistry and biopharmaceutics perspective.

The application has not been considered by the Pharmaceutical Subcommittee (PSC) of the ACPM because no issues requiring their expertise were identified during the chemistry and quality evaluation.

III. Nonclinical findings

Assessment

- The sponsor has applied to register Seasonique, consisting of tablets containing levonorgestrel and ethinyloestradiol in combination (150 µg/30 µg) and tablets containing ethinyloestradiol as a single agent (10 µg). The product is proposed to be used as an oral contraceptive, with the dosing regimen involving once daily administration of one tablet on a continuous 91 day cycle: the levonorgestrel/ethinyloestradiol tablet is taken for 84 consecutive days followed by the ethinyloestradiol tablet for 7 days. Formulation details are given.
- This application represents a major variation (change in dosage regimen) for levonorgestrel/ethinyloestradiol. Existing levonorgestrel/ethinyloestradiol containing contraceptive products are taken on a 28 day cycle (21 days active phase with levonorgestrel and ethinyloestradiol in combination; 7 days placebo or tablet free phase). The sponsor proposes that the removal of an inactive phase provides greater ovarian suppression, reduces the potential for hormone withdrawal symptoms and improves the bleeding profile.
- The maximum daily dose of the two active ingredients is not increased with Seasonique compared with existing approved therapies.
- The nonclinical dossier comprised 68 literature references, but was not a formal literature based submission. The nonclinical data do not cover the change in dosing regimen. It is acceptable that this be addressed from clinical data only, particularly given that hormonal regulation of reproductive function is highly species specific, making extrapolation of animal data to humans difficult.
- The literature references submitted by the sponsor in the nonclinical dossier have been offered to support statements proposed for the PI document that deviate from text approved in existing Australian PIs for levonorgestrel/ethinyloestradiol containing products. These deal with Distribution, Metabolism, Use in Pregnancy, Genotoxicity and Carcinogenicity.
- There are no nonclinical objections to the registration of Seasonique. The PI, though, should be amended as described. In particular, known or suspected pregnancy should be added as a contraindication.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Ethinyloestradiol and levonorgestrel are synthetic steroid hormones with predominantly oestrogenic and progestogenic actions, respectively.

The submission proposes registration of the two dosage forms and strengths as described above:

- an oral tablet containing the combination of ethinyloestradiol 30 µg and levonorgestrel 150 µg
- an oral tablet containing ethinyloestradiol 10 µg.

Clinical rationale

COCs were originally developed in the 1960s using a 28 day cycle because it was felt appropriate to mimic the physiological ovarian cycle in which menstruation occurs when progesterone levels fall at the end of the luteal phase in the absence of conception having occurred. Typically, 21-22 days of a combined oestrogen/progestogen tablet are given followed by a 6-7 day HFI during which withdrawal bleeding occurs. Early COC formulations contained oestrogen doses of or equivalent to ethinyloestradiol in the 50-100 µg range. These were associated with significant side effects, particularly thromboembolic disorders, and subsequent product development involved lowering the ethinyloestradiol (or equivalent) dose to the 20-30 µg level as in the applicant product.

Following the acceptance of COCs as a safe and effective method of contraception, they came into use also as a means of regulating the menstrual cycle in women with a variety of cycle disorders involving irregular, excessively frequent or infrequent menstruation. The practice then developed of giving COC tablets continuously as a form of medically induced amenorrhoea for women with medical conditions which worsened during menstruation. The principle of using this method for women desiring contraception but without medical indications for menstrual suppression is well summarised by Edelman,[3] who cites the proven safety and acceptability of the approach as encouraging compliance with the contraceptive regimen and having the potential to improve women's quality of life.

The rationale for using 7 days administration of the low 10 µg dose of ethinyloestradiol in place of the HFI is outlined and is based on the hypothesis that this will maintain suppression of the hypothalamic-pituitary-ovarian axis during the HFI, thus limiting the possibility of escape ovulation so that contraceptive efficacy might be improved or at least maintained. It is also postulated that this regimen might reduce the likelihood of hormone withdrawal symptoms during the HFI, and improve the pattern of withdrawal bleeding.

Guidance

The relevant EMA guideline[4] (adopted by the TGA) is noted.

[3] Edelman A. Menstrual nirvana: amenorrhoea through the use of continuous oral contraceptives. *Curr Womens Health Rep.* 2: 434 (2002).
[4] European Medicines Agency, "Guideline on clinical investigation of steroid contraceptives for women (EMEA/CPMP/EWP/519/98 Rev 1)", 27 July 2005.

Contents of the clinical dossier

The submission contained the following clinical information:

- 6 clinical pharmacology studies, including 2 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- 1 pivotal efficacy/safety study.
- 4 other efficacy/safety studies.

Paediatric data

The submission did not include paediatric data. The product is not intended for paediatric use. Note however that data has been submitted in relation to adolescent females (study DR-105-202) and comments on the potential for use in this age group are included in this report.

Good clinical practice

The submitted studies all state compliance with the required guidelines and appear to have been conducted accordingly.

Pharmacokinetics

Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies are presented in this report. Table 1 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 1: Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Multi-dose	10216207
	Bioequivalence† - Single dose	10416204

† Bioequivalence of clinical trial versus market formulation.

Evaluator's conclusions on pharmacokinetics

The sponsor has provided sufficient data to extend existing knowledge on the pharmacokinetics (PK) of the product's constituent substances to cover the particular characteristics of the applicant product Seasonique and describes these adequately in the draft PI.

Pharmacodynamics

Studies providing pharmacodynamic data

Summaries of the pharmacodynamic (PD) studies are presented in this report. Table 2 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 2: Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on inhibition of ovarian function	DR-PSE-310
		DR-PSE-312
	Effect on suppression of ovulation	DR-105-101
Secondary Pharmacology	Effect on blood coagulation	PSE-HSP-203

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacodynamics

The submitted studies provide evidence that suppression of ovarian function and inhibition of ovulation is maintained throughout the extended cycle form of administration of this oral contraceptive formulation (OCP) formulation, and that replacement of the hormone free interval with 7 days of 10 µg ethinyloestradiol improves these PD actions in a way which would be consistent with improved contraceptive efficacy.

Dosage selection for the pivotal studies

The entire development program for Seasonique described by the sponsor employs the dosage combination of ethinyloestradiol 30 µg and levonorgestrel 150 µg for continuous daily administration over the 84 days of active combined oestrogen/progestogen administration, this being a dosage of well-established efficacy in the various 21 or 22 day cycle COC formulations in existing use as described above. The dosage of 10 µg ethinyloestradiol for the 7 day period of administration occupying days 84-91 of the Seasonique cycle finds support in the PD studies described. In pivotal study PSE-301, this 10 µg dose over days 84-91 of the cycle is compared with a 30 µg dose.

Efficacy

Studies providing efficacy data

Study PSE-301 was a pivotal efficacy study. This was a two arm, randomised, multicentre open label study conducted at 36 US sites between April 2002 and April 2004. The primary objective was to demonstrate efficacy and safety of two 91 day cycle extended regimen COC formulations: DP3-84/10 (Seasonique), and a similar product DP3-84/30 as described above, in which the HFI was replaced with a 30 µg rather than 10 µg ethinyloestradiol dose. In each arm, subjects were to take the assigned treatment for one year (four 91 day cycles). Secondary objectives were to observe the incidence or severity of "hormonal related symptoms" during the treatment period and to observe the number of reported days of scheduled (withdrawal) and unscheduled (breakthrough) menstrual bleeding and/or spotting.

Study PSE-302 was another efficacy study. This four arm, randomised, multicentre, open label study was conducted at 7 US sites over the same timeframe (April 2002-2004) as the

pivotal efficacy Study PSE 301. With a much smaller planned study population (400, 100 per arm) its objectives were to provide supportive efficacy data well as additional safety data in the form of endometrial biopsies to be performed before and at the end of the study; the safety data also included analysis of the bleeding profiles and this is detailed.

Evaluator's conclusions on efficacy

All contraceptive methods, including COCs, have a failure rate, the measurement of which is the incidence of on-treatment pregnancy (Pearl index). The measurement of efficacy of any novel COC is therefore how its failure rate compares with that of other established COC products. For this particular submission, the question is whether the extended cycle regimen differs either positively or negatively in efficacy by comparison with a standard 28 day cycle formulation containing the same constituent substances. In this respect the pivotal efficacy Study 301 has a high dropout rate, and poor compliance in some subjects. There are multiple confounding factors which contribute to the failure rate of oral contraceptive regimens. The most important of these are compliance and the demography of the study population including cultural (for example, level of sexual activity) and biological (for example, incidence of obesity) factors. As is discussed at length in the clinical overview, it is well documented that there is a substantial difference in failure rate between US and European populations.[5] A published comparison of US and European studies using the same methodology showed an approximately four fold higher failure rate in the US.[6]

The pivotal trial is of low quality (50% dropouts) but was the same pivotal trial used to register the product in Canada, US and various EU countries.

Safety

Studies providing safety data

Pivotal efficacy study

In the pivotal efficacy Study PSE-301, safety was evaluated by assessment of adverse events (AEs), tabulation of concomitant medications, recording of vital signs and physical examination when appropriate, and the performance of routine laboratory tests as specified in the protocol. These included plasma lipids in view of the known effects of OCPs on these parameters.

AEs were reported during scheduled study visits and also during regular monthly telephone contacts, their severity graded and likely relationship to study medication recorded by the site investigator. In this and in all of the other studies reported below, the subjects' menstrual bleeding pattern was regarded as an AE of particular interest and recorded as days of either spotting or bleeding, the distinction being made on the basis of whether sanitary protection was required.

Non-pivotal efficacy study

One non-pivotal efficacy study provided safety data, as follows:

- Study PSE-302 provided data on 372 subjects randomised to 4 treatment groups as described above. In addition to safety data collected using the same protocol as the

[5] Dinger JC, et al. Oral contraceptive effectiveness according to body mass index, weight, age, and other factors. *Am J Obstet Gynecol.* 201: 263.e1-9 (2009).
[6] Dinger J, et al. Effectiveness of oral contraceptive pills in a large U.S. cohort comparing progestogen and regimen. *Obstet Gynecol.* 117: 33-40 (2011).

pivotal study, endometrial histology was assessed by biopsies obtained before and at the end of the study and is reported as a safety issue of special interest.

Other studies evaluable for safety only

Study DR-PSE-304

This was a long term extension study which enrolled subjects completing Studies PSE-301 and PSE-302. Although designed to document up to 5 years of use, the maximum duration documented in the report is three years, achieved by 116 of the 320 subjects treated. Approximately midway through the study, in June 2005, and following completion of the pivotal study PSE-301, all subjects were switched to the DP3-84/10 (Seasonique) formulation as this, rather than the DP3-84/30 formulation, had been selected for marketing application in the US.

Studies DR-PSE-305 and DR-PSE-306

These two studies were performed to evaluate efficacy of Seasonique for the treatment of cyclical pelvic pain in adult and adolescent females respectively. Safety data were collected using the same protocol as used in the pivotal study. In Study 305, subjects were randomised to receive either Seasonique (n = 91) or Portia (n = 82), a 28 day cycle formulation using the same constituent substances and doses as Seasonique. In Study 306, 47 subjects were randomised to Seasonique and 48 to placebo.

Study DR-105-202

This study was performed to assess the effect on bone mineral density (BMD) of Seasonique administered to adolescent females (age 12-18 years inclusive) over a period of 12 months. 421 subjects were randomised to Seasonique, and 412 to Lessina, a 28 day cycle OCP formulation containing ethinyloestradiol 20 µg/levonorgestrel 100 µg. In addition there was a control group of 437 subjects who received no treatment. Although strictly not fitting this description, the BMD data are presented as an AE of special interest below.

Clinical pharmacology studies

Safety data collected during the PK/PD studies are included in the overall safety data pool but contribute a relatively small component.

Patient exposure

In the clinical development program, the majority of exposure to DP3-84/10 (Seasonique) and comparator products, was of up to 12 months duration and occurred in pivotal study 301 and supporting study 302. Cumulative exposure of all subjects treated in these studies is shown in Table 3.

Table 3: Cumulative exposure.

28-Day Month on Study	DP3-84/30 (N=1108) N	%	DP3-84/10 (N=1101) N	%	DP3-25/30 (N=89) N	%	Nordette (N=93) N	%
> 0	1108	100.0	1101	100.0	89	100.0	93	100.0
≥ 1	1025	92.5	1026	93.2	84	94.4	85	91.4
≥ 2	914	82.5	946	85.9	80	89.9	79	84.9
≥ 3	841	75.9	879	79.8	76	85.4	77	82.8
≥ 4	760	68.6	798	72.5	70	78.7	73	78.5
≥ 5	717	64.7	756	68.7	63	70.8	71	76.3
≥ 6	679	61.3	710	64.5	60	67.4	67	72.0
≥ 7	627	56.6	657	59.7	54	60.7	64	68.8
≥ 8	603	54.4	638	57.9	50	56.2	61	65.6
≥ 9	588	53.1	613	55.7	48	53.9	58	62.4
≥ 10	559	50.5	580	52.7	46	51.7	54	58.1
≥ 11	548	49.5	568	51.6	45	50.6	52	55.9
≥ 12	531	47.9	557	50.6	45	50.6	50	53.8
Completed the Study	519	46.8	546	49.6	44	49.4	47	50.5

Comment: the exact number of completed cycles is not given in the study report. However, from the above table it is estimated that total exposure of all treatment groups is approximately 1600 woman-years, or 20,800 completed 28 day cycles (evaluator calculation). Of this, approximately 50% represents exposure to Seasonique itself and the remainder exposure to similar 30 µg ethinyloestradiol/150 µg levonorgestrel products, the majority to DP3-84/30 which also has an 84 day cycle.

Longer term exposure to both 84 cycle day preparations occurred in study DR-PSE-304, as shown in Table 4.

Table 4: Longer term exposure.

Years on Study	DP3-84/30 (N=147) N	%	DP3-84/10 (N=173) N	%	Total (N=320) N	%
> 0	147	100.0	173	100.0	320	100.0
≥ 1	113	76.9	131	75.7	244	76.3
≥ 2	79	53.7	94	54.3	173	54.1
≥ 3	43	29.3	42	24.3	85	26.6
≥ 4	0	0.0	0	0.0	0	0.0
Completed the Study	57	100.0	59	100.0	116	100.0

A total of 244 subjects completed one year of treatment, 173 completed two years, and 116 three years. Total exposure was equivalent to 8,292 28 day cycles, 4411 of which were for the Seasonique product, equivalent to 638 woman-years (339 for Seasonique).

In the supportive safety studies, exposure to Seasonique is estimated as follows:

- DR-105-202: 296 woman-years
- PSE-305: 32 woman-years
- PSE-306: 16 woman-years

In summary, overall exposure to the applicant product Seasonique in the submitted studies is approximately **1160 woman-years, equivalent to 15,080 28 day cycles** (evaluator calculation) accompanied by a similar amount of exposure to comparator products containing the same constituents and mostly also with the 84 day cycle of continuous exposure.

Post marketing data

A summary of post marketing data is provided. In the period up to December 2013 (7.5 years following market release in the US) 1.55 million prescriptions were written for

Seasonique. Exposure was estimated at 385,101 woman-years. During this period 466 AEs were reported, most commonly some form of vaginal bleeding. Based on the sales data the sponsor estimates the rate of such reported bleeding as being 0.06%. A tabulation of adverse events by system organ class notified to the FDA in the period up until June 2010 is provided. This lists 363 reported events covering a wide clinical spectrum. None seem unexpected in the context of long term COC use.

Evaluator's conclusions on safety

The overall safety of Seasonique is well demonstrated by the included studies, on an adequate number of subjects. The pattern of AEs demonstrated in the included studies matches that associated with existing approved COC preparations of the same formulation as Seasonique.

Use of Seasonique is associated with a menstrual bleeding profile which differs from that associated with conventional 28 day cycle COCs; the extended cycle regimen means that there are less frequent scheduled withdrawal bleeds, but there is an increased frequency of intermenstrual, unscheduled bleeding which is most prominent during the first year of use and has in the included studies been associated with a significant discontinuation rate. This is not a safety issue but may affect the acceptability of the product for women who use it. The bleeding is not associated with any adverse effects on the endometrium.

The inclusion in the application of safety data on adolescent post menarchal subjects is appropriate as the proposed indication "use as an oral contraceptive" may include its use in that population.

Risk of venous thromboembolic events (VTEs) and arterial thromboembolic events (ATEs) are too uncommon/rare to make any sort of estimate from the pre-market clinical trial.

There was one case of venous thrombotic event reported with Seasonique in a patient having a mutation in factor V Leiden. One case of arterial thrombotic event was reported with DP3-84/30 in a patient with predisposing thrombotic risk factors. No conclusion could be drawn from single cases.

First round benefit-risk assessment

First round assessment of benefits

The benefits of Seasonique in the proposed usage are:

- Contraception with a level of reliability commensurate with that of most currently available oral contraceptive formulations.
- Reduction in the frequency of menstruation from once per month to four times per year.
- For those users who have troublesome menstruation related symptoms, a reduction in frequency of those symptoms also (note that this is not a benefit claimed by the sponsor, but is a likely one).

First round assessment of risks

The risks of Seasonique in the proposed usage are:

- The established, well documented risks of oral contraceptive formulations containing oestrogen/progestogen doses at the level used in Seasonique (for example, an increased risk of venous thromboembolic disorders).

- Unpredictable intermenstrual bleeding, with the possibility of being in the small proportion of users in whom this occurs to an unacceptable degree.
- VTE/ATE are too rare to be characterised in the pre-market data. It is unknown whether VTE/ATE is more or less common with Seasonique than with other combined hormonal contraceptive (CHC) with shorter cycles.

First round assessment of benefit-risk balance

At this point in time, pending the sponsor's response and further TGA evaluation, the benefit-risk balance of Seasonique, given the proposed usage, is favourable.

First round recommendation regarding authorisation

At this point in time, and pending the sponsor's response and further TGA evaluation, no objection is seen to approval of the application.

Clinical questions

- Is there any information about whether the risk of the uncommon adverse reactions of VTE and ATE is greater or lesser with Seasonique compared to 30 day cycle CHC?
- Are any post marketing studies of the comparative risk of VTE or ATE planned?

Second round evaluation

Details are provided in Attachment 2.

Second round benefit-risk assessment

The sponsor has provided satisfactory responses to the questions posed.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU-RMP Version 4.0 (dated 17 April 2015, Data Lock Point 28 February 2015) with Australian Specific Annex (ASA) Version (dated 28 April 2015), which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4: Ongoing safety concerns.

Summary – Ongoing Safety Concerns	
Important identified risks	Venous thromboembolic events
	Arterial thromboembolic events
	Liver tumours (benign and malign)

Summary – Ongoing Safety Concerns	
	Cycle disorders
	Depression
	Effects on hereditary angioedema
Important potential risk	Breast cancer
	Cervical dysplasia/cancer
	Decreased bone density in adolescents
	Weight increase
	Unrecognised pregnancies and the consequences of delayed pregnancy detection
	Detrimental effects on Crohn's disease and ulcerative [NB: add 'colitis']
Important missing information	Return to fertility
	Use in women under 18 years of age
	Long-term safety

RMP reviewer comment

Notwithstanding to the evaluation of the non-clinical and clinical aspects of the Safety Specification, the summary of safety concerns is considered incomplete in the context of this application. From review of the advice presented in the PI:

- 'Diabetes mellitus with vascular involvement' is listed as a Contraindication, with Precautions also highlighting potential risks in this population. 'Diabetes mellitus with vascular involvement' should be included as an important potential risk to better monitor this population in future reporting.
- 'Pancreatitis or a history thereof if associated with severe hypertriglyceridemia' is listed as a Contraindication, with Precautions also highlighting this risk. 'Pancreatitis or a history thereof if associated with severe hypertriglyceridemia' should be included as an important potential risk.
- There are Precautions relating to hypertension: If, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. 'Pre-existing or non-responsive hypertension' should be included as an important potential risk.

'History of migraine with focal neurological symptoms' is listed as a Contraindication. As this particular identified safety concern is shared across oral contraceptives, it is acceptable for this to not be included in the Summary.

Chloasma is identified as an effect associated with COCs in women predisposed to the condition. There are Precautions related to this outcome in the PI, in addition to it being identified as a 'serious adverse event' (SAE). While it is noted that chloasma may be

distressing to patients, it is not considered to meet the definition of a serious adverse event and therefore does not require inclusion in the Summary.

There is a typographical error in the summary, being omission of the word 'colitis' after the term 'ulcerative'. This should be corrected in the next RMP submission. Further, the RMP documentation refers to tumours as both 'malign' and 'malignant' – the sponsor should be consistent with this descriptor in future RMP submissions.

Pharmacovigilance plan

In the EU-RMP, the sponsor proposes routine and additional pharmacovigilance for the identified/potential risks and missing information presented in the Summary of Safety Concerns (Table 5).

Table 5: Safety concerns and planned actions

Safety concern	Planned action(s)
Important identified risks	
Venous thromboembolic events (VTEs)	Routine pharmacovigilance Specific follow-up questionnaire Post-authorisation safety study (PASS) [see following text]
Arterial thromboembolic events (ATE)	Routine pharmacovigilance Specific follow-up questionnaire
Liver tumours (benign and malign)	Routine pharmacovigilance
Cycle disorders	Routine pharmacovigilance
Depression	Routine pharmacovigilance Specific follow-up questionnaire
Effects on hereditary angioedema	Routine pharmacovigilance
Important potential risks	
Breast cancer	Routine pharmacovigilance Specific follow-up questionnaire
Cervical dysplasia/cancer	Routine pharmacovigilance
Decreased bone density in adolescents	Routine pharmacovigilance
Weight increase	Routine pharmacovigilance
Unrecognised pregnancies and the consequences of delayed	Routine pharmacovigilance Specific follow-up questionnaire on delayed

Safety concern	Planned action(s)
pregnancy detection	pregnancy detection
Detrimental effects on Crohn's disease and ulcerative colitis	Routine pharmacovigilance
Missing information	
Return to fertility	Routine pharmacovigilance Specific follow-up questionnaire on fertility disorders
Use in women under 18 years of age	Routine pharmacovigilance
Long-term safety	Routine pharmacovigilance

The sponsor has identified the VTE Post-Authorisation Safety Study (PASS) as planned for 4Q2015, with final analysis anticipated when data covering at least three years is available. It is identified in the EU-RMP that that the VTE PASS may also address other risks as secondary endpoints (for example, ATE [including acute myocardial infarction, ischaemic stroke, and cerebrovascular accidents], fertility, breast cancer and other gynaecological cancers, pregnancy outcomes, and delayed pregnancy detection). A synopsis of the protocol was provided with the submission.

Samples of the follow-up questionnaires were provided with the submission and are considered appropriate for the reporting of targeted AEs.

RMP reviewer comment

There is no definite objection to the pharmacovigilance plan proposed by the sponsor in the context of this application. It is noted from the ASA that there are no additional pharmacovigilance activities planned for the Australian market not reported in the EU-RMP.

The sponsor has indicated that interim analysis of the PASS study will be conducted one year after the date of launch in Europe or reimbursement of Seasonique. The sponsor should provide the results of this interim analysis in the future when available.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities (that is, PI labelling) for all identified/potential safety concerns and missing information.

The proposed risk minimisation activities are discussed further below.

RMP reviewer comment

The sponsor's conclusions with regards to proposed risk minimisation activities are considered reasonable in the context of this submission. Risk minimisation activities are further discussed below.

Reconciliation of issues outlined in the RMP report

The following section summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the TGA RMP reviewer, and the RMP reviewer's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Sponsor response

Safety considerations were raised by the nonclinical and clinical evaluation reports that may of the relevance for the RMP are related to risks of VTE and ATE. These risks are already recognised as important identified risks, and are adequately characterised in the RMP.

No additional safety considerations were raised by the nonclinical and clinical evaluators that are of the relevance for the RMP.

Teva is planning to conduct a retrospective longitudinal cohort study to assess the safety of short and long term use of Seasonique. Primary objective of this post marketing authorisation safety study (PASS) is to compare the incidence rates of VTE in women exposed to Seasonique with women exposed to 28 day cycle levonorgestrel containing combined oral contraceptives (COCLNG). ATE was set as a secondary objective of the study.

Evaluator's comment

The sponsor's response is noted and is satisfactory from a RMP perspective.

Recommendation #2 in RMP evaluation report

'Diabetes mellitus with vascular involvement' is listed as a Contraindication in the PI, with Precautions also highlighting potential risks in this population. 'Diabetes mellitus with vascular involvement' should be included as an important potential risk in the Summary of Safety Concerns.

Sponsor response

Diabetes mellitus with vascular involvement is a condition considered as a risk factor for development of ATE;[7] however, the primary risk being ATE.

ATE and VTE are already included as important identified risks in the RMP and a PASS is planned to further evaluate and characterise these risks. The PI states that diabetes mellitus is one of medical conditions which have been associated with adverse vascular events.

PI also states that diabetic women should be carefully observed, particularly in the early stage of COC use, which is considered sufficient. Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low dose COCs (containing < 50 µg ethinyloestradiol).

Additionally, specific follow-up questionnaire distribution will be triggered in case of spontaneously received case reports directly from healthcare professionals and patients/consumers for all events under SMQ "Embolic and thrombotic events, arterial". According to the questionnaire, patients will be asked if they have history of diabetes and the medical history will be taken into account when assessing the risk of ATE.

[7] Alison Brayfield, ed. (2014). Martindale: The Complete Drug Reference (38th ed.). London: Pharmaceutical Press.

Therefore, we consider that the currently proposed safety concerns and pharmacovigilance activities in the RMP are sufficient.

Evaluator's comment

The sponsor's response is satisfactory from a RMP perspective.

Recommendation #3 in RMP evaluation report

'Pancreatitis or a history thereof if associated with severe hypertriglyceridemia' is listed as a Contraindication in the PI, with Precautions also highlighting this risk. 'Pancreatitis or a history thereof if associated with severe hypertriglyceridemia' should be included as an important potential risk in the Summary of Safety Concerns.

Sponsor response

Pancreatitis or a history thereof if associated with severe hypertriglyceridemia was established as exclusion criteria in the clinical trial development plan, and therefore is included as a contraindication. One of the risk factors for developing pancreatitis is hyperlipidaemia which is a known metabolic effect of all COCs and does not represent a new safety concern. According to Martindale,[8] the oestrogen component increases triglycerides, but decreases low density lipoproteins, whereas the progestogen component tends to decrease high density lipoproteins and increase low-density lipoproteins, particularly if it is androgenic (19-nortestosterone-derived) progestogens. It is known that hypertriglyceridemia may cause chronic pancreatitis and high serum triglyceride level (usually more than 1000 mg/dL) can trigger acute pancreatitis. Epidemiological evidence also suggests that the composition of blood lipids may be one of several risk factors involved in the aetiology of various adverse cardiovascular events.[9]

Pancreatitis is listed in the RMP as an important pharmacological class effect. Only 2 cases of pancreatitis were reported so far, both in patients included in clinical trial program and were co-reported with cholelithiasis, which is another risk factor for developing pancreatitis. One patient had a history of cholelithiasis, while the other experienced cholelithiasis followed by pancreatitis while being treated with Seasonique. Therefore, the first event was reported as not related to Seasonique, but the possible relationship could not be excluded in the second case. Nevertheless, there was no sufficient information to indisputably confirm the link. Both events resulted in recovery at the time of reporting. No cases of pancreatitis were reported in post marketing.

Routine pharmacovigilance activities are considered sufficient to monitor this risk of hypertriglyceridemia and associated risk factors and possible outcomes including pancreatitis. The PI states that women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when using COCs. Seasonique is contraindicated in patients with pancreatitis or a history thereof if associated with severe hypertriglyceridemia.

Additionally, since hypertriglyceridemia is considered to be a risk factor for development of ATE and, according to a specific questionnaire for ATE, patients that experienced ATE will be asked if they have history of dyslipoproteinemia, hypertriglyceridemia or pancreatitis (as the history of pancreatitis may also be related to hypertriglyceridemia).

Therefore, we consider that the currently proposed safety concerns in the RMP are sufficient.

Evaluator's comment

The sponsor's response is satisfactory from a RMP perspective.

[8] Alison Brayfield, ed. (2014). Martindale: The Complete Drug Reference (38th ed.). London: Pharmaceutical Press.
[9] Micromedex Insights, 2015.

Recommendation #4 in RMP evaluation report

There are Precautions in the PI relating to hypertension: If, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. 'Pre-existing or non-responsive hypertension' should be included as an important potential risk in the Summary of Safety Concerns.

Sponsor response

Hypertension is a well-known metabolic effect of all COCs (due to their steroid structure) and is considered primarily to be a risk factor for development of cardiovascular effects, including ATE,[10] and not a new safety concern.

The PI states that the risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with hypertension. Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The risk is sufficiently communicated in the product information and routine pharmacovigilance are considered sufficient to monitor this risk. Additionally, when an event related to ATE is reported, specific questionnaire will be triggered and patients will be checked for history of hypertension. If confirmed, the history of hypertension will be considered when assessing the report.

Therefore, we consider that the currently proposed safety concerns and monitoring as described in the RMP are sufficient.

Evaluator's comment

The sponsor's response is satisfactory from a RMP perspective.

Recommendation #5 in RMP evaluation report

There is a typographical error in the Summary, being omission of the word 'colitis' after the term 'ulcerative'. This should be corrected in the next RMP submission. Further, the RMP documentation refers to tumours as both 'malign' and 'malignant' – the sponsor should be consistent with this descriptor in future RMP submissions.

Sponsor response

Teva agrees to apply the requested revisions. New version of the EU RMP has already incorporated these changes. Revised version 4.0 of the EU RMP (sign off date 23 Nov 2015) was submitted in EU on 21 December 2015 and is also appended to this response. Since the last version was not approved, the versioning 4.0 remains in the document, but internally this version is considered to be 4.0.1 to distinguish it from the previous version.

Evaluator's comment

The sponsor's response is noted.

Recommendation #6 in RMP evaluation report

The sponsor has indicated that interim analysis of the PASS study will be conducted one-year after the date of launch in Europe or reimbursement of Seasonique. The sponsor

[10] Alison Brayfield, ed. (2014). Martindale: The Complete Drug Reference (38th ed.). London: Pharmaceutical Press.

should commit to providing the results of this interim analysis in the future when available.

Sponsor response

Teva is committed to providing the results of this interim analysis in the future when available. The updated study milestones are presented in the revised version of the RMP.

Evaluator's comment

The sponsor's response is noted.

Recommendation #7 in RMP evaluation report

The SmPC has a clear Contraindication for use of Seasonique 'in association with herbal remedy St. John's Wort (hypericum perforatum).' As relevant to Australia, this Contraindication should be included to enhance safe use of Seasonique.

Sponsor response

The PI has been updated to include "In association with herbal remedy St. John's Wort (hypericum perforatum" in the Contraindications section).

Evaluator's comment

The sponsor's response is satisfactory from a RMP perspective. This issue remains for final determination by the Delegate.

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

There are no outstanding issues in relation to the RMP for this submission.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

Clinical evaluation report

There were no comments on the Safety Specification of the RMP in the Round 1 clinical evaluation. In the follow-up evaluation, the clinical evaluator noted the following:

> *A total of nine questions regarding the RMP were put to the sponsor in the Section 31 request. These did not arise from my clinical evaluation report. I presume that there has been a separate RMP evaluation report and that the author of this will examine the sponsor's responses. The questions posed address specific issues regarding diabetes, pancreatitis and hypertension and otherwise refer to some requested changes in the product information. The sponsor's responses appear to me to address the issues in a satisfactory way and to detail changes which have been made to the PI and CMI as recommended.*

Nonclinical evaluation report

The nonclinical evaluation report makes no specific reference to the safety specification of the RMP.

Key changes to the updated RMP

EU-RMP Version 4.0 (dated 17 April 2015, DLP 28 February 2015) with Australian Specific Annex Version (dated 28 April 2015) has been superseded by:

EU-RMP Version 4.0 (as Teva internal version 4.0.1, dated 23 November 2015, DLP 20 November 2015) and Australian Specific Annex (dated 28 April 2015)

In their response to the TGA Section 31 Request, the sponsor provided a RMP updated with minor amendments (Version 4.0 [as Teva internal version 4.0.1], dated 23 November 2015, DLP 20 November 2015; see sponsor response to recommendation 5 in table below). There are no significant changes to the safety specification, pharmacovigilance activities, or risk minimisation activities in the revised version.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

Implement RMP Version 4.0 (as Teva internal Version 4.0.1, dated 23 November 2015, DLP 20 November 2015) with ASA Version (dated 28 April 2015) and any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluator advised that there are no further outstanding issues that require resolution and approval can be recommended from a pharmaceutical chemistry and biopharmaceutics perspective.

Nonclinical

The nonclinical evaluator did not have any objections to the registration of Seasonique. The sponsor has provided an amended PI as per nonclinical evaluator's recommendations.

Clinical

Pharmacology

The general PK of the two constituent substances ethinyloestradiol and levonorgestrel are well established given the multiple formulations containing this combination previously registered in Australia.

There were two PK studies submitted. The single dose Study 10416204 established bioequivalence of the clinical trial formulation and the to-be-marketed formulation in the US. A study comparing the US marketed formulation and the proposed formulation in Australia has not been conducted; the clinical evaluator noted the formulations to be identical in active and excipient components, except for the coating colour.

Study 10216207 was an open label multiple dose study to evaluate the single and steady state PK of a combination tablet containing ethinyloestradiol 30 µg and levonorgestrel 150 µg. Subjects received a single tablet of ethinyloestradiol 30 µg/levonorgestrel 150 µg for

84 days, followed by a single tablet of ethinyloestradiol 30 µg for 7 days. Steady state for both ethinyloestradiol and levonorgestrel was reached by Day 21 with no evidence of accumulation thereafter.

PD studies

There were four PD studies:

- Study PSE-310 was an open label, randomised study to evaluate the suppression of the pituitary-ovarian axis with a COC regimen in which the HFI is replaced by 7 days administration of ethinyloestradiol 10 µg. The three treatment arms were: Seasonique (84 days ethinyloestradiol 30 µg/levonorgestrel 150 µg followed by 7 days of ethinyloestradiol 10 µg), Seasonale (84 days ethinyloestradiol 30 µg/levonorgestrel 150 µg followed by 7 days placebo) or Portia (21 days ethinyloestradiol 30 µg/levonorgestrel 150 µg followed by 7 days placebo, for three cycles). All subjects then received a follow-up Portia cycle during which follicular growth was assessed. Given the small sample size (n = 10-12 subjects per arm), the clinical evaluator considered the study exploratory; however, serum FSH, LH, and particularly oestradiol remained more suppressed in the Seasonique arm compared with Seasonale. Further, there was evidence of greater suppression on follicular growth into the follow-up Portia cycle with Seasonique compared with Seasonale.
- Study PSE-312 was a similar study, evaluating the suppression of the pituitary-ovarian axis with a 28 day cycle COC preparation (containing ethinyloestradiol 30 µg/levonorgestrel 150 µg) with ethinyloestradiol 10 µg taken for 7 days during the usual HFI, for two cycles. Again this was a small study, and a similar pattern of hormonal suppression as seen in Study PSE-301 was observed, although a statistically significant difference between the active and placebo groups was observed for inhibin-B and oestradiol. The clinical evaluator noted suppression of ovarian activity by ethinyloestradiol 10 µg during the HFI can occur with conventional 28 day COCs as well as with an extended cycle regimen.
- Study DR105-101 was an open label, uncontrolled, single cohort study to evaluate ovulation inhibition with a 91 day course of Seasonique. Ovarian activity was assessed by transvaginal ultrasound and serum FSH, LH, oestradiol and progesterone at intervals of 28, 28 and 35 days. Whilst there were two instances of ovulation during interval 3, overall ovarian activity was more suppressed during intervals 2 and 3, with progressive fall in levels of LH, FSH, oestradiol and progesterone through to Day 84. Both FSH and LH levels rose during Days 85-91, suggesting some escape from gonadotrophin suppression in this period despite the ethinyloestradiol 10 µg dose.
- Study PSE-HSP-203 was an open label randomised study comparing the effect on haemostatic parameters of Seasonique with two standard 28 day COC preparations in healthy female subjects. During the six month treatment period subjects received either Seasonique (two 91 day cycles), Minidril (21 days of combination ethinyloestradiol 30 µg and levonorgestrel 150 µg followed by 7 days of no treatment, for a total of six cycles) or Marvelon (21 days of combination ethinyloestradiol 30 µg/desogestrel 150 µg followed by 7 days of no treatment, for a total of six cycles). The primary efficacy parameter was the procoagulatory marker prothrombin fragments 1 + 2, measured at 3 months and 6 months. There was a similar degree of rise in prothrombin fragments for Seasonique compared with Minidril, with a much greater rise (bordering on statistical significance) compared with Marvelon. There were various changes noted for other procoagulatory and anticoagulatory variables. The clinical evaluator concluded the use of the extended cycle regimen did not constitute an additional thromboembolic risk when compared to the standard 28 day cycle regimen.

Efficacy

There were two efficacy studies:

Pivotal Study PSE-301

Study PSE-301 was a two arm, randomised, multicentre, open label study conducted in the USA from 2002-2004 to demonstrate the efficacy and safety of two 91 day cycle extended regimen COC formulations taken for one year in women desiring pregnancy prevention. The two treatment arms were:

- DP3-84/10 [Seasonique]: 84 days combination of ethinyloestradiol 30 µg/levonorgestrel 150 µg followed by 7 days ethinyloestradiol 10 µg.
- DP3-84/30: a similar product comprising 84 day of ethinyloestradiol 30 µg /levonorgestrel 150 µg and ethinyloestradiol 30 µg for 7 days.

The study population included sexually active women aged 18-40 years at risk of pregnancy who had a history of OC use prior to enrolment (continuous users), no prior history of OC use (fresh starts) or history of OC use, but not within the six months prior to enrolment (prior users). Women with contraindications to COC use were excluded. The majority of subjects were Caucasian (79.8%), with mean age 27.4 years and mean BMI 26.9 kg/m^2. 23.5% were smokers.

There were 2049 subjects randomised in a 1:1 ratio to either DP3-84/10 (n = 1025 randomised, n = 1013 treated) or DP3-84/30 (n = 1024 randomised, n = 1006 treated). Subjects received study medication for one year (four 91-day cycles).

The primary efficacy endpoint was the on-treatment pregnancy rate (those pregnancies for which the conception date was on or after the date of first dose of study medication, but no more than 14 days after the last dose of combination medication), based on the Pearl Index, and calculated on the pregnancy intent-to-treat cohort (PITT; all subjects 18-35 years old with at least one complete cycle of treatment).

The calculation was also made on other cohorts including the compliant use cohort (all complete cycles for patients in the PITT cohort in which no other birth control method was used and the patient was deemed to be compliant during the cycle (where non-compliance was defined as all cycles in which a patient skipped two or more consecutive pills or had a pattern of substantial non-compliance [an overall compliance of less than 80%] with study medication, or used a prohibited concomitant medication that may interact with OC therapy). 97.6% of subjects had ≥ 80% compliance.

Secondary efficacy outcome was calculation of pregnancy rate using life table analysis.

With regard to sample size, the clinical evaluator stated:

> *the study report states that determination of method failure is "generally based" on exposure of approximately 10,000 women-months (28 day cycles), hence the selection of approximately 1000 subjects per treatment group.*

Results of Study 301

There was a high rate of discontinuation throughout the study, with 979 subjects (48.5% of those treated) completing the study. The main reasons for discontinuation were adverse event (18.0%), lost-to-follow-up (14.8%) and patient decision (12.0%). Pregnancy accounted for 23 (1.1%) discontinuations, although the Clinical Evaluator noted 68 randomised subjects became pregnant during the study. For 23 cases pregnancy was the primary reason for discontinuation, with the Clinical Evaluator commenting the remaining 48 pregnancies occurred in patients reporting other primary reasons for discontinuation such as 'personal decision'.

Of the 364 (18.0%) of subjects who discontinued due to an AE, 147 (40%) withdrew due to bleeding and/or spotting episodes (generally balanced between the two treatment groups); the clinical evaluator noted 40 (16%) of those subjects who discontinued due to 'personal decision' also cited bleeding and/or spotting as at least part of the reason for the decision.

Primary efficacy analysis

There were 20 on-treatment pregnancies (n= 13 in the DP3-84/30 cohort and n = 7 in the DP3-84/10 cohort). Of these 20 pregnancies, 11 were considered 'compliant-use' (n = 8 and n = 3 in the in the DP3-84/30 and DP3-84/10 arms respectively). The clinical evaluator noted the remaining 48 pregnancies occurred either when the study drug was no longer taken, or when the Investigator deemed the subject to have been non-compliant. The results of the Pearl Index calculations are shown and reproduced below in Table 6.

Table 6: Safety concerns and planned actions.

	DP3-84/30		DP3-84/10	
	N	Pearl Index	N	Pearl Index
PITT (Excluding Other BCMs)	581	2.74	621	1.27
PITT (all Complete Cycles)	668	1.95	708	0.92
PITT (Compliant-Use)	560	2.26	607	0.78
ITT (all Complete Cycles)	771	1.66	799	0.80

The clinical evaluator commented:

> *The study report postulates that the values for Pearl Index in the category PITT (excluding other BCMs) may be an overestimate as the excluded cycles include those in which subjects have recorded using a condom for prevention of sexually transmitted disease rather than as a BCM. This argument is plausible but it is also possible that the higher estimate in this cohort is a real finding indicative of the product's "typical use" efficacy, at least in this population.*
>
> *The apparent difference between the two treatment groups is not explained, would not have been predicted on the basis of pharmacodynamic data, and is most likely a chance finding reflecting the relatively small numbers of pregnancies involved.*

The results of the life table analysis were comparable with the Pearl Index calculations.

The clinical evaluator concluded the pivotal trial to be of low quality with 50% dropouts, however, noted this was the pivotal study supporting registration in the US, Canada and various EU countries.

Supportive Study PSE-302

Study PSE-302 was a 4 arm, randomised, open label, multicentre, 12 month study to provide supportive efficacy as well as additional safety data (endometrial biopsies).

The study protocol, inclusion and exclusion criteria were similar to the pivotal efficacy study PSE-301. The study population comprised 400 women (n = 100 per arm). The treatment arms were DP3-84/10 (Seasonique, n = 95 treated) and DP3-84/30 (n = 95 treated) as above, as well as the two additional arms:

- DP3-25/30 (a 28-day cycle preparation of 25 days of ethinyloestradiol 30 µg/levonorgestrel 150 µg followed by 3 days of ethinyloestradiol 30 µg; n = 89 treated)
- Nordette (commercially available 28-day cycle preparation of ethinyloestradiol 30 µg/levonorgestrel 150 µg administered for 21 days, followed by 7 days of placebo tablets; n = 93 treated),

The sponsor states the sample size of 400 patients was chosen to provide adequate information regarding endometrial biopsy findings; assuming a discontinuation rate of 50%, 40 patients per treatment arm was considered a reasonable number for the clinical evaluation of endometrial biopsy results.

The study was completed by 46 (48.4%), 40 (42.1%), 44 (49.4%) and 47 (50.5%) of subjects in the DP3-84/10, DP3-84/30, DP3-25/30 and Nordette cohorts, respectively.

The treatment failure rates for the compliant use subset of the PITT are shown. While the numbers of on-treatment pregnancies (n = 1 for each of the DP3-84/10, DP3-84/30 and Nordette treatment groups, and n = 0 for the DP3-25/30 group) were small, the clinical evaluator noted the results were consistent with the contraceptive efficacy data of the pivotal Study PSE-301.

Safety

The majority of exposure to DP3-84/10 and comparators in the clinical development program was of up to 12 months duration and occurred in the pivotal Study PSE-301, and supportive Study PSE-302. Longer term safety data were provided by Study PSE-304, a non-randomised extension study of a subset of subjects who had completed studies PSE-301 and PSE-302. This study included 320 subjects treated with DP3-84/10 (n = 173 treated) or DP3-84/30 (n = 147 treated; subsequently changed to DP3-84/10 approximately midway through the study when this formulation was selected for marketing approval in the US). This study was to provide data for 5 years follow up, although the study report provided data for maximum duration of 3 years (n = 116 subjects treated).

Additional safety data were provided by Studies DR-PSE-305, DR-PSE-306 and DR-105-202.

The clinical evaluator calculated the overall exposure to Seasonique in the submitted studies to be approximately 1160 woman-years (or 15, 080 completed 28-day cycles), with a similar amount of exposure to comparator products (mostly to the similar 84 day cycle product DP3-84/30).

In the pivotal study PSE-301, the most frequent treatment emergent AE was inter-menstrual bleeding (11.6%), and menorrhagia. Other AEs included those commonly experienced with COC preparations (nausea, acne NOS, weight increased, headache and breast tenderness) and were mostly balanced across the DP3-84/10 and DP3-84/30 treatment groups (Table 7).

Table 7: Study PSE-301: Treatment-related AEs occurring in 2% or more of all treated patients (Safety).

MedDRA System Organ Class and Preferred Term	DP3-84/30 (N=1013) N	%	DP3-84/10 (N=1006) N	%	Total (N=2019) N	%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Intermenstrual bleeding	120	11.85	114	11.33	234	11.59
Menorrhagia	74	7.31	56	5.57	130	6.44
Breast tenderness	21	2.07	28	2.78	49	2.43
Dysmenorrhoea	33	3.26	28	2.78	61	3.02
INVESTIGATIONS						
Weight increased	33	3.26	44	4.37	77	3.81
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Acne NOS	35	3.46	44	4.37	79	3.91
GASTROINTESTINAL DISORDERS						
Nausea	30	2.96	31	3.08	61	3.02
Abdominal distension	18	1.78	22	2.19	40	1.98
PSYCHIATRIC DISORDERS						
Mood swings	27	2.67	30	2.98	57	2.82
NERVOUS SYSTEM DISORDERS						
Headache NOS	28	2.76	27	2.68	55	2.72

The AE profile of the supportive studies was generally similar.

In the pivotal Study PSE-301, 6.7% of Seasonique subjects, and 8.5% of DP3-84/30 subjects discontinued due to AEs, mostly due to inter-menstrual bleeding or menorrhagia; other discontinuations were due to various symptoms including headache, acne, and breast tenderness.

AEs of special interest

Scheduled and unscheduled bleeding

Scheduled (withdrawal) bleeding is bleeding/spotting during the 7 days of ethinyloestradiol monotherapy or placebo. Unscheduled bleeding is bleeding/spotting which occurs during the active combination oestrogen/progestogen administration.

In pivotal Study PSE-301, the total number of days of total bleeding and/or spotting per cycle was noted to be highest in the first cycle, diminishing by cycle 3 and 4 (Table 8).

Table 8: Total number of days of total bleeding and/or spotting per cycle (complete cycles only) – patients with at least one complete cycle of treatment (ITT).

Treatment Group	Cycle	N	Mean (SD)	Min	Q1	Median	Q3	Max	Median Per Patient-Month
DP3-84/30	1	739	18.5 (15.63)	0	6	14	28	77	4.3
	2	609	15.3 (14.49)	0	5	10	23	89	3.1
	3	513	12.6 (12.26)	0	4	9	18	66	2.8
	4	421	11.9 (12.39)	0	3	7	16	75	2.2
DP3-84/10	1	758	17.7 (14.50)	0	6	14	26	80	4.3
	2	625	12.6 (11.47)	0	4	9	18	70	2.8
	3	533	10.0 (10.10)	0	3	7	14	57	2.2
	4	446	10.3 (10.37)	0	3	6.5	14	65	2.0

The clinical evaluator noted the mean (and SD) values to be much higher than the median, suggesting higher rates of bleeding for a substantial proportion of subjects. In terms of unscheduled bleeding (generally considered less acceptable to users), this pattern was again observed; by cycle 4 the mean (SD) number of days of unscheduled bleeding/spotting per 91 day cycle had reduced to 7.6 (9.37) [3.2 (5.4) days for bleeding only], versus median value per patient month of 0.3.

Study PSE-302 provided a comparison of the bleeding profile of Seasonique with conventional 28-day cycle preparation of ethinyloestradiol 30 µg/levonorgestrel 150 µg (Nordette). The duration of withdrawal bleeding was similar for Seasonique and Nordette (mean 2.33 days versus 2.07 days), with the frequency of withdrawal bleeds over 12 months of use much less on Seasonique as expected (4 times versus 13 times with Nordette). Whilst the total number of unscheduled bleeding days over the 12 months was almost double for Seasonique users compared with Nordette users (mean 20.1 versus 11.3 days), the clinical evaluator noted these conclusions were based on the first year of use, with the data suggesting an improvement in bleeding (particularly unscheduled bleeding) over the course of the first year.

Longer term data available from Study PSE-304 suggest a progressive reduction in unscheduled bleeding over the 3 years (12 cycles), although the clinical evaluator commented the higher mean and median values in earlier cycles may be due in part to subjects dropping out due to unacceptable bleeding.

Endometrial histology

In Study PSE-302, endometrial biopsies were obtained from 372 randomised subjects prior to treatment, and from 226 subjects during the last treatment cycle (n = 63 [66.3%] Seasonique subjects). There were no cases of endometrial hyperplasia or other abnormal unexpected findings reported.

BMD

Study DR-105-202 was a Phase II, randomised, open label, controlled study to assess the effects on bone mineral density (BMD) of Seasonique (n = 421) compared with a 28-day cycle COC formulation (Lessina; ethinyloestradiol 20 µg/levonorgestrel 100 µg; n = 412) and control (n = 437) in adolescent females (aged 12-18 years) over 12 months. The primary efficacy variable was the percent change in baseline to 12 months in lumbar spine BMD. Non-inferiority of Seasonique to control was demonstrated (as was non-inferiority of the active comparator Lessina to control).

Post marketing experience

The sponsor stated over 1.5 million prescriptions were written for Seasonique from product launch (September 2006) up to December 2013, with an estimated exposure of 385,101 woman-years. There were 466 AEs reported, most commonly related to vaginal bleeding. A tabulation of AEs by SOC reported to the FDA up to 29 June 2010 was provided. There were 363 AEs reported across a variety of SOCs, with the most frequent reported AE metrorrhagia (n = 60). The clinical evaluator did not consider any AE to be unexpected in the context of long term COC use.

With regard to VTE and ATE, the following events were reported:

- Vascular disorders SOC: DVT (n = 2), thrombosis (n = 4).
- Respiratory, thoracic and mediastinal disorders SOC: pulmonary embolism (n = 6), pulmonary thrombosis (n = 2).
- Nervous system disorders SOC: cerebral thrombosis (n = 2), cerebrovascular accident (n = 2)

The clinical evaluator noted VTE/ATE are too rare to be characterised by pre-market data, commenting the risk of same with Seasonique compared with other COCs with shorter cycles is unknown. In terms of post-market data, those events relating to VTE / ATE reported to the FDA (by preferred term), as noted above, were few (n = 18 in total). As part of the Round 2 response, the sponsor stated there is a post-marketing authorisation study planned to be conducted in the EU to compare the incidence of VTE (primary objective) and ATE (secondary objective) in users of Seasonique with users of a 28-day

cycle levonorgestrel containing COC (Study protocol submitted to EU Authorities November 2015). Interim analysis to be conducted at 1 year post-launch in Europe, and final analysis when data for at least three years post launch available.

Risk management plan

Summary of safety concerns are shown in Table 9.

Table 9: Summary of safety concerns

Important identified risks	VTE ATE Liver tumours (benign and malignant) Cycle disorders Depression Effect on hereditary angioedema
Important potential risks	Breast cancer Cervical dysplasia/cancer Decreased bone density in adolescents Weight increase Unrecognised pregnancy Detrimental effects on Crohn's disease and ulcerative colitis
Missing information	Use in women younger than 18 Long term safety

There are no additional pharmacovigilance or risk minimisation activities proposed for Australia.

As outlined above under "Safety", a PASS is planned in EU to compare rates of VTE in women exposed to Seasonique versus those on a levonorgestrel containing CHC with a 28 day cycle. The protocol is currently under development. ATE and breast cancer are secondary outcomes.

Risk-benefit analysis

Delegate's considerations

The contraceptive efficacy of Seasonique has been adequately established. The safety of combined oral contraceptives is well characterised. No new safety concerns were identified in the clinical trials for Seasonique. The post marketing safety data from US and Canada are reassuring.

Whether Seasonique has a higher risk of VTE/ATE (rare events) compared to "standard" combined hormonal contraceptives (with a 28 day cycle) is not known. This current uncertainty will be addressed by statements in the PI/CMI. The uncertainty will be reduced via a PASS in the EU. Long term safety on breast cancer is also not completely elucidated and will be addressed in the planned PASS (secondary endpoint).

Proposed action

The Delegate has no reason to say, at this time, that the application for Seasonique should not be approved for registration.

Pending further advice, at this point in time, based on the available data, efficacy and safety have been satisfactorily established.

Request for ACPM advice

The committee is requested to provide advice on any issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

No issues or questions were raised in the Delegate's overview.

Please find included in this response dossier the following requested documents:

- Updated 1.11.1 Foreign regulatory status
- Updated 1.11.2 EU Summary of Product Characteristics
- 1.11.2 US Prescribing Information
- 1.11.2 Canada Product Monograph
- 5.3.6 PSUR (13 January 2015 to 13 July 2015)

As noted, the products approved in US and Canada have different formulations (different colourant only) as well as different manufacturing sites.

Please refer to sequence 0002 for the latest versions of the PI and CMI. No changes have since been made to these documents.

The first PSUR for Seasonique covering the period from 13 January 2015 to 13 July 2015 is provided. No serious unexpected adverse drug reactions were reported in this period.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Seasonique film coated tablet, containing 150 µg levonorgestrel/30 µg ethinyloestradiol and film coated tablet containing 10 µg ethinyloestradiol of ethinyloestradiol to have an overall positive benefit-risk profile for the indication:

Seasonique is indicated for the use as an oral contraceptive

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI.

Specific advice

The ACPM advised the following in response to the Delegate's request for advice on this submission.

The ACPM advised that the data submitted including the long term post marketing data, supported efficacy and safety. The ACPM noted that this product may provide improved contraception for some patients due to decreased escape ovulation. The ACPM noted that

there did not seem to be any significant coagulation effects compared with the standard 28 day regimen. The dropout rate was attributed to bleeding irregularities, which decreased with time on the medication.

The ACPM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Seasonique levonorgestrel/ethinyloestradiol 150 µg/30 µg film coated tablets blister pack and ethinyloestradiol 10 µg film coated tablets blister pack composite pack

The approved indication for this therapeutic good is:

> *Seasonique is indicated for use as an oral contraceptive.*

Specific conditions of registration applying to these goods

- The Seasonique levonorgestrel/ethinyloestradiol + ethinyloestradiol EU RMP, version 4.0, (as Teva internal Version 4.0.1, dated 23 November 2015, DLP 20 November 2015) with ASA version dated 28 April 2015 and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Attachment 1. Product Information

The PI approved for Seasonique at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au