20 November 2014
EMA/CHMP/24607/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Pursuant to Article 29(4) of Directive 2001/83/EC

Seasonique and associated names

International Non-proprietary Names: levonorgestrel and ethinylestradiol

Procedure no: EMEA/H/A-29/1392

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure

1.1. Decentralised procedure (DCP) and CMD(h) 60 day procedure

Teva Pharma submitted to France on 26 March 2012 an application for decentralised procedure (DCP) for Seasonique and associated names, a fixed combination of levonorgestrel 150 µg/ ethinylestradiol 30 µg and ethinylestradiol 10 µg film-coated tablets, intended to be used as an extended regimen oral contraceptive.

The application was submitted to the reference Member State (RMS), France and the concerned Member States (CMS) Austria, Belgium, Germany, Italy, Poland, Romania, Slovakia and Slovenia.

The Decentralised procedure FR/H/516/01/DC started on 24 May 2012.

On day 210, Germany's major issues on efficacy remained unsolved; hence the procedure was referred to the CMD(h), under Article 29, of Directive 2001/83/EC, by France on 15 November 2013. The CMD(h) 60-day procedure was initiated on 2 December 2013.

Day 60 of the CMD(h) procedure was on 30 January 2014 and since there could be no agreement the procedure was referred to the CHMP.

1.2. Notification of an official referral for arbitration

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC to the CHMP was made by France on 03 February 2014. Germany raised public health objections to the granting of a marketing authorisation for Seasonique and associated names on the ground that the contraceptive efficacy had not been sufficiently demonstrated. The objecting Member State (OMS) argued that the bootstrap method proposed by the applicant to calculate the 95% CI of the overall Pearl Index (PI) was not valid. The OMS also raised concerns regarding the acceptability of the bleeding pattern associated with the use of Seasonique and associated names.

2. Scientific discussion during the referral procedure

2.1. Introduction

Seasonique is a 91-day extended regimen oral contraceptive (OC) consisting of a fixed dose combination of levonorgestrel 150 µg/ ethinylestradiol 30 µg for 84 days followed by ethinylestradiol 10 µg film-coated tablets for 7 days. Levonorgestrel (LGN) is a progestogen known to inhibit ovulation, whilst the low dose ethinylestradiol (EE), an estrogen, ensures control over ovarian follicular suppression and provides stability to the endometrium in order to minimise breakthrough bleeding. Due to the low estrogen content, the preparation belongs to the so-called low-dose combined oral contraceptives (COCs).

Both active substances are already authorised in this combination, at this dosage and at a lower dosage (LGN 100 µg/ EE 20 µg). Seasonique is authorised in some countries outside the European Union (EU).

The decentralised marketing authorisation application was submitted under Article 28(3) of Directive 2001/83/EC in accordance with Article 10b of Directive 2001/83/EC. The proposed indication for Seasonique was "*oral contraception*".

During the decentralised procedure, the OMS was of the view that the contraceptive efficacy of Seasonique had not been sufficiently demonstrated. Indeed, as in the pivotal study PSE-301 the classic Poisson method failed to reach adequate precision for the 95% CI of the overall Pearl Index (PI) point estimate for Seasonique in women aged 18-35 years (point estimate 0.76, 95% CI of 0.16 – 2.22), the Applicant presented additional analyses using a bootstrap method for calculation of the 95% CI. With this method, chosen post-hoc, adequate precision with regard to requirements for hormonal contraceptive methods in the CHMP Guideline on Clinical Investigation of steroid contraceptives in women (EMEA/CPMP/EWP/519/98 Rev. 1) would just be reached (depending on the specific bootstrap simulation) with a point estimate of 0.76 and a 95 % CI of (0.0 - 1.76). In addition, the OMS considered that the bleeding pattern is not favourable and could not rule out a potential impact on treatment compliance and contraceptive efficacy.

The decentralised procedure was closed on day 210, with most of the CMS agreeing with the conclusions of the RMS except Germany which raised a potential serious risk to public health. A referral was thus triggered at the CMDh. Further analyses including both arms (DP3-84/30 (higher dose of EE than Seasonique in the last 7 days of the cycle) and DP3-84/10 (Seasonique)) of the pivotal study PSE-301 and the supportive study PSE-302 did not provide a more reliable estimation of contraceptive efficacy of Seasonique despite the increase in sample size and resulted in a higher PI of 1.67 (95% CI 0.91 - 2.80). Thus, the major concern raised by Germany could not be solved during the CMDh referral and the issue was therefore referred to the CHMP.

2.2. Critical evaluation

The clinical development program for Seasonique included two phase III randomised clinical trials conducted in the United States, the pivotal study PSE-301 and a supportive study, PSE-302, specifically designed to assess endometrial biopsy results and included a limited number of cycles of exposure available for the PI evaluation.

Table 1. Overview of the phase III studies included in the clinical development program for Seasonique

Study	Design	Treatment group	Number of Subjects	Primary endpoint
PSE-301 (Pivotal study)	Two-arm, randomised, open-label, multicentre	DP3-84/30: LNG 0.15 mg and EE 0.03 mg 84 days followed by 7 days EE 0.03 mg for four 91-day cycles	1013	Prevention of pregnancy (Pearl Index)
		DP3-84/10 (Seasonique): LNG 0.15 mg and EE 0.03 mg 84 days followed by 7 days EE 0.01 mg	1006	

Study	Design	Treatment group	Number of Subjects	Primary endpoint
PSE-302 (supportive study)	Four-arm, randomised, open-label, comparator, multicentre	DP3-84/30: LNG 0.15 mg and EE 0.03 mg 84 days followed by 7 days EE 0.03 mg for four 91-day cycles	95	Safety evaluation using results of endometrial biopsy evaluations
		DP3-84/10 (Seasonique): LNG 0.15 mg and EE 0.03 mg 84 days followed by 7 days EE 0.01 mg for four 91-day cycles	95	
		DP3-25/30: LNG 0.15mg and EE 0.03 mg 25 days followed by 3 days EE 0.03mg for thirteen 28-day cycles	89	
		Nordette: LNG 0.15mg and EE 0.03 mg 25 days followed by 7 days placebo for thirteen 28-day cycles	93	

2.2.1. Contraceptive efficacy

In the pivotal study PSE-301, 3 pregnancies were observed for Seasonique in 1,578 91-day cycles in 621 women aged 18-35 years, resulting in an overall PI of 0.76 with a 95% CI of 0.16 – 2.22 using the Poisson model. As mentioned, the applicant presented during the DCP additional analysis with the bootstrap method reaching adequate precision for contraceptive methods as shown by the 95 % CI: 0.0 – 1.76, however concerns were raised regarding the validity of this post-hoc analysis. The CHMP requested advice from the Biostatistics Working Party (BSWP) on the validity of this method in the present case. The CHMP supported the position of the BSWP, which considered that the bootstrap method is generally inappropriate for calculating confidence intervals for a PI; even more so in this example where it was not pre-specified, and was employed only after negative results were seen for the more conventional analysis. The PI calculated with the Poisson method was therefore considered acceptable taking into account that the extended regimen in Seasonique is only a minor modification of an existing product.

Indeed the LNG 150 µg/ EE 30 µg hormonal combination has been approved as a contraceptive in the EU for over 35 years and its efficacy is well documented.

Moreover the applicant conducted a non-comparative pharmacodynamic (PD) study, DR-105-101 during one extended cycle of 91 days (84 days of LNG/EE, followed by 7 days of EE only). For the analysis, this period was split in two 28-day and a 35-day periods. Ovulation occurred in two subjects (5.71% of the women) during the second 28-day period, one whom also ovulated in the third period, resulting in an overall ovarian activity rate of 2.86 (95% CI: 0.78 -7.22) over a period of 91 days. The absence of a comparator arm was considered justified given that the mechanism of action of this hormonal combination in this dose is well known, that the only differences between Seasonique and existing LNG/EE combination products are the treatment duration (84 days versus 21 days, respectively) and the administration of 10 µg EE during the last 7 days of the cycle instead of an hormone free interval (HFI), respectively. Additionally several published pharmacodynamic studies demonstrated that the degree of ovulation inhibition is increased with a shorter HFI. Levels of follicle-

stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and inhibin B were suppressed more effectively when the duration of the HFI was shortened from 7 days to 3 or 4 days per 28-day treatment cycle (Willis, 2006 [1]). This more pronounced suppression was also demonstrated with 24/4 drospirenone 3 mg/EE 2 µg regimen compared to a standard 21/7 regimen (Klipping, 2008 [2]), for the 24/4 oral regimen with a nomegestrol acetate/17b-estradiol compared to the 21/7 regimen (Christin-Maitre, 2011 [3]), and for a 23-day regimen of 0.075 mg gestodene/20 µg EE compared with a 21-day regimen (Spona, 1996 [4]). It has also been shown in the literature that the elimination of the HFI is associated with a better inhibition of the ovarian activity. A published study with 3 different combined oral contraceptives (COCs) arms, reported that women treated with a continuous 28-day regimen had more pronounced follicular suppression than women who were either supplemented with 5 days of 10 µg EE or had a 7-day HFI (Schlaff, 2004 [5]). Another published pharmacodynamic study reported a continuous COC regimen with Levonorgestrel/EE and norgestimate/EE to result in a more effective follicular suppression than the same COC dosing regimen with a monthly 7-day HFI (Birtch, 2006 [6]). Based on the results from these published clinical studies, Seasonique is expected to have a greater control over ovulation, leading in turn to a higher contraceptive efficacy compared to standard 21/7-day LNG/EE COCs and therefore a comparative pharmacodynamic study against standard 21/7-day LNG/EE COCs is not considered mandatory.

Moreover standard 21/7-day COCs containing LGN 150 µg/ EE 30 µg are widely used and, according to the respective product information in some Member States, the cycle can be extended to 2-months, without HFI. Thus the absence of HFI is not considered to decrease the contraceptive efficacy and the CHMP considered that the well documented contraceptive efficacy with 28-day LGN 150 µg/ EE 30 µg combination can be extrapolated to the Seasonique regimen.

The results obtained in clinical trials with Seasonique are further supported by post-marketing data. From data outside the EU, since the first authorisation in 2006 until December 2013, while the estimated exposure is 385,901 women-years, only 10 pregnancies were reported resulting in a pregnancy reporting rate of 0.0026 %.

In addition, a 1-year retrospective study in women 15 to 40 years of age, showed that reported pregnancy rates were lower with extended regimen OC (84/7) than with 'standard' regimens (21/7 and 24/4). This study included 52,664 women (mean age, 27.3 years) in the 84/7 vs. 21/7 analysis (n=26,332 in both groups) and 50,694 (mean age, 27.8 years) in the 84/7 vs. 24/4 analysis (n=25,347 in both groups). One-year pregnancy rates were statistically significantly lower with the 84/7 regimen compared with the 21/7 (4.4% vs. 7.3%; p<0.0001) and with the 24/4 (4.4% vs. 6.9%, p<0.0001) regimens. Statistically significantly higher rates of pregnancy with 21/7 and 24/4 regimens compared to the 84/7 regimen (p<0.0001) were also seen in the 2- and 3-year cohorts (Howard, 2014 [7]). Some CHMP members considered that this publication is not acceptable as proof of

[1] Willis SA, Kuehl TJ, Spiekerman AM, Sulak PJ. Greater inhibition of the pituitary-ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. Contraception 2006;74:100-3.
[2] Klipping C, Duijkers I, Trummer D, Marr J. Suppression of ovarian activity with a drospirenone-containing oral contraceptive in a 24/4 regimen. Contraception. 2008 Jul;78(1):16-25. Epub 2008 May 27.
[3] Christin-Maitre S, Serfaty D, Chabbert-Buffet N, Ochsenbein E, Chassard D, Thomas JL. Comparison of a 24-day and a 21-day pill regimen for the novel combined oral contraceptive, nomegestrol acetate and 17{beta}-estradiol (NOMAC/E2): a double-blind, randomized study. Hum Reprod. 2011 Mar 18.
[4] Spona J, Elstein M, Feichtinger W, Sullivan H, Lüdicke F, Müller U, Düsterberg B. Shorter pill-free interval in combined oral contraceptives decreases follicular development. Contraception. 1996 Aug; 54(2):71-7.
[5] Schlaff WD, Lynch AM, Hughes HD, Cedars MI, Smith DL. Manipulation of the pill-free interval in oral contraceptive pill users: the effect on follicular suppression. Am J Obstet Gynecol. 2004 Apr;190(4):943-51.
[6] Birtch RL, Olatunbosun OA, Pierson RA. Ovarian follicular dynamics during conventional vs. continuous oral contraceptive use. Contraception. 2006 Mar;73(3):235-43.
[7] Howard B, Trussell J, Grubb E, Lage MJ.Comparison of pregnancy rates in users of extended and cyclic combined oral contraceptive (COC) regimens in the United States: a brief report. Contraception 89 (2014) 25–27.

contraceptive efficacy of extended cycle regimens as this type of study is prone to various kinds of confounders. Indeed, duration of use of the different COCs was not known and in consequence, it was unknown whether the women were still using the COC when the pregnancy was diagnosed or whether the observed pregnancies were intended. As stated by the authors, it was also not known whether the women used these COCs for other reasons than prevention of pregnancy. In spite of these limitations, in view of the majority this publication at least does not support a reduced contraceptive efficacy associated with the 84/7 regimen.

Of note, combined analyses including both arms (DP3-84/30 (higher dose of EE than Seasonique in the last 7 days of the cycle) and DP3-84/10 (Seasonique regimen)) of the pivotal study PSE-301 and the supportive study PSE-302 resulted in a higher PI of 1.67 (95% CI 0.91 - 2.80). However in the DP3-84/30 arm of study PSE-301, for 3 out of the 9 pregnancies included in the analysis as 'on-treatment', drug accountability could not be performed; indeed, based on the available data, these pregnancies might be considered 'off-treatment'. Study PSE-302 included a limited number of cycles of exposure and was not designed for PI evaluation. For these reasons the CHMP did not consider this higher PI as relevant in the assessment of the efficacy of Seasonique.

In conclusion, although the PD study did not include a comparative arm, based on extensive results from published clinical studies and considering that the extended regimen in Seasonique is a minor modification from existing products, Seasonique is expected to have a greater control over ovulation compared to the existing LNG/EE combination products for which the efficacy is well documented. PD data showed that the ovarian inhibiting efficacy of Seasonique is within the range of that observed for other approved combined hormonal contraceptives. Moreover the pregnancy rate observed in the phase III clinical trial was relatively low (PI<1), and no signal of a reduced efficacy was detected in the large experience obtained post-marketing. Therefore the CHMP considered the efficacy of Seasonique adequately demonstrated.

2.2.2. Bleeding pattern

The bleeding pattern of Seasonique was compared to the standard 21/7-day cycle regimen (Nordette, LNG 150 µg/ EE 30 µg and 7-day HFI) in the study PSE 302 (see table 1 above). Although, based on women who completed one year of treatment, discontinuation due to bleeding/spotting adverse events was more frequent in the Seasonique group (7.4%) than the comparator group (1.1%), the mean total number of days of bleeding/spotting (including scheduled and unscheduled) per patient month was similar, i.e. 4.4 days for both Seasonique and the comparator. Hence the applicant was asked to conduct additional analyses of the bleeding pattern based on three extrapolation rules to include women who prematurely discontinued treatment and to extrapolate those data to the total planned study duration of PSE-302 of one year.

The total number of days with bleeding/spotting within the planned study duration of 1 year was higher for the Seasonique group than for the comparator group (mean 61-62 vs. 55-56, depending on the extrapolation rule). As expected, due to the extended regimen, the total number of scheduled bleeding/spotting within the planned study duration was 3 times lower for Seasonique than for the comparator (mean 11 vs. 33). On the contrary, the total number of unscheduled bleeding/spotting days was twice higher for Seasonique than for the comparator (mean 53 vs. 24).

Similar number of patients reported unscheduled bleeding of each severity: 64 (80.0%) and 69 (78.4%) for light bleeding, 42 (52.5%) and 42 (47.7%) for moderate bleeding and 14 (17.5%) and 13 (14.8%) for heavy bleeding, for Seasonique and Nordette groups, respectively.

In line with these findings, the laboratory results demonstrated that the unscheduled bleeding/spotting profile with Seasonique did not lead to clinically significant changes.

The overall treatment compliance for all treated patients was ≥ 97% in the pivotal study and ≥ 98% in the supportive study. Comparable withdrawal rates were observed in Study PSE-302 for the Seasonique group (51.6%) and for the comparator group (49.5%). Comparable withdrawal rates, including discontinuation due to adverse events, were also observed in an open label, randomised phase II study comparing Seasonique (34.5%) to two 28-day OC (35.2% and 39.1%) in 265 women for 8 months.

In conclusion, as shown in study PSE-302 the total number of bleeding/spotting days was higher for Seasonique than for the comparator, Nordette. The increased number of unscheduled bleeding/spotting days with Seasonique appeared not to have an effect on compliance compared to other 21/7-day OC. This was further supported by the absence of anaemia or clinically important changes in the laboratory results compared to the 21/7-day COC. Therefore the CHMP considered that the bleeding pattern with Seasonique neither constitutes a safety issue for women nor impairs the contraceptive efficacy and adequate information in this respect is already included in the proposed product information.

2.3. Risk management plan (RMP)

A RMP was submitted and agreed upon during the preceding Decentralised Procedure on Seasonique. No additional modifications were made by the CHMP.

2.4. Recommendation

Having considered all the data submitted by the applicant, and the view of the BSWP, the CHMP considered that the contraceptive effectiveness of Seasonique was adequately demonstrated. The CHMP also considered that the bleeding pattern associated with the use of Seasonique neither constituted a safety issue, nor impaired efficacy.

2.5. Conclusions and benefit risk assessment

Whereas,

- The Committee considered the notification of the referral triggered by France under Article 29(4) of Directive 2001/83/EC. Germany considered that the granting of the marketing authorisation constitutes a potential serious risk to public health.

- The Committee reviewed all the data submitted by the applicant in support of the efficacy of Seasonique and associated names in oral contraception as an extended regimen.

- The Committee is of the opinion that the available data is supportive of the efficacy of Seasonique and associated names as an extended regimen of an existing combined oral contraceptive.

- The Committee is also of the opinion that the bleeding pattern associated with the use of Seasonique and associated names constitutes neither a safety issue nor impairs the contraceptive efficacy, and that adequate information is included in the proposed product information in this regard.

the CHMP was of the opinion that the benefit/risk ratio of Seasonique and associated names is considered to be favourable. The CHMP issued a positive revised opinion recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP revised opinion. The divergent positions are appended to this report and to the revised opinion.

Appendix 1

Divergent positions

Referral under Article 29(4) of Directive 2001/83/EC

Procedure No: EMEA/H/A-29/1392

Seasonique and associated names (INN: levonorgestrel and ethinylestradiol)

Divergent statement

Some CHMP members considered that the contraceptive efficacy of Seasonique and associated names has not been sufficiently demonstrated for the following reasons:

- The clinical trial data did not provide sufficient reassurance regarding the contraceptive efficacy of the proposed extended regimen. The conventional Poisson Method did not meet the usual guideline requirements for a new contraceptive method (EMEA/CPMP/EWP/519/98 Rev. 1, 27 July 2005).

- The Seasonique extended cycle regimen is considered as a new contraceptive method, not as a minor modification of a conventional 28-day cycle COC containing levonorgestrel and ethinylestradiol. Another flexible extended cycle regimen (Yvidually, EMEA/H/A-29/1330) was approved within the EU based on adequate precision of the estimation of the Pearl Index as required for a new contraceptive method in accordance with section 3.1 of the above mentioned CHMP guideline and a database much larger than that submitted for Seasonique. The extension of the conventional 28-day cycle regimen per se is considered as clinically more relevant than the different types of extended cycle regimens. Extended cycle regimens may be associated, as was observed for Seasonique, with an increased rate of irregular bleeding and an increased discontinuation rate with the necessity of changing the contraceptive method. Such aspects could, among other things, affect contraceptive efficacy. Therefore, Seasonique should not be classified as a minor modification of an existing product. In addition, with the approval of Seasonique, the consistency of regulatory standards for approval of contraceptives appears doubtful.

- Combined analyses including both treatment arms of the pivotal study PSE-301 or from studies PSE-301 and PSE-302 resulted in higher Pearl Indices (1.58 or 1.67, respectively) and higher upper limits of the 95% CI (2.76 or 2.80, respectively) and were therefore even less convincing. Combining treatment arms to increase statistical power was considered reasonable since the only difference between them was the dose of ethinylestradiol (EE) (10 µg vs. 30 µg) during the last 7 days of the 91-day treatment cycle, which is not expected to have an impact on contraceptive efficacy. It is acknowledged that in the DP3-84/30 arm of study PSE-301 for 3 of 9 pregnancies included in the analysis, drug accountability could not be performed. Nevertheless, these 3 pregnancies should be included in a conservative analysis of contraceptive efficacy.

- The pharmacodynamic study DR-105-101 was small and uncontrolled but also casts doubt on adequate suppression of ovarian activity since 2 of the 35 subjects ovulated during one Seasonique 91-day cycle (6% with an upper limit of the 95% CI of 19%) with one subject having even 2 ovulations. A controlled study on ovarian activity was not conducted. Thus, the requirement for a minor modification of an existing product according to section 3.2 of the above mentioned CHMP guideline, i.e. demonstration of “at least an equivalent effect on ovarian function compared with the existing product” is not met. Equivalence regarding ovarian inhibition can only be concluded based on an adequately powered randomised study, not based on historical comparisons. According to published literature, ovarian inhibition is improved with a shortened hormone-free interval or extended cycle regimens, compared to conventional cycle regimens with a 7-day

hormone-free interval. Thus, the finding of 3 ovulations in the small PD study with Seasonique it is even more concerning.

- Post-marketing data from spontaneous reporting cannot reliably establish efficacy of an oral contraceptive (OC) and the 1-year retrospective study by Howard and Colleagues has relevant limitations precluding firm conclusions on the efficacy of extended regimen OCs.

- Finally, efficacy data obtained for the conventional 28-day cycle cannot simply be extrapolated to a 3-month extended regimen. In addition, the occasional or exceptional extension of a conventional 1-month cycle of levonorgestrel (LNG)/EE containing OCs (e.g. Microgynon) to 2 months included in the product information of some member states does not allow conclusions on the contraceptive efficacy of a generally 3-month extended regimen.

- The bleeding pattern of Seasonique is considered unfavourable as, compared to Nordette (conventional cycle LNG/EE OC), the overall days with bleeding/spotting were not reduced and may even be higher leading to a relevantly higher rate of study discontinuations for this reason. While days with scheduled bleeding/spotting were reduced, days with unscheduled bleeding/spotting were doubled, which may have an impact on treatment compliance and contraceptive efficacy.

CHMP members expressing a divergent opinion:

Agnes Gyurasics (HU)	20 November 2014	Signature: ……...
Alar Irs (ET)	20 November 2014	Signature: ……...
Bruno Sepodes (PT)	20 November 2014	Signature: ……...
Daniela Melchiorri (IT)	20 November 2014	Signature: ……...
Harald Enzmann (DE)	20 November 2014	Signature: ……...
Jan Mueller-Berghaus (co-opted)	20 November 2014	Signature: ……...
Jens Heisterberg (DK)	20 November 2014	Signature: ……...
Outi Mäki-Ikola (FI)	20 November 2014	Signature: ……...
Ondřej Slanař (CZ)	20 November 2014	Signature: ……...