Annex II

Scientific conclusions and grounds for positive opinion presented by the European Medicines Agency

Scientific conclusions

Overall summary of the scientific evaluation of Seasonique and associated names (see Annex I)

Seasonique is a 91-day extended regimen oral contraceptive 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 Objecting Member State (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 Concerned Member States (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.

Critical evaluation

The clinical development program for Seasonique included two phase III randomised clinical trials, the pivotal study PSE-301 and a supportive study, PSE-302, specifically designed to assess endometrial biopsy results, which were performed in the United States.

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 coverage probability properties 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 10µg 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). 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), for the 24/4 oral regimen with a nomegestrol acetate/17b-estradiol compared to the 21/7 regimen (Christin-Maitre, 2011), and for a 23-day regimen of 0.075 mg gestodene/20 µg EE compared with a 21-day regimen (Spona, 1996). 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). 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). 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). Some CHMP members considered that this publication is not acceptable as proof of contraceptive efficacy of extended cycle regimens as this type of study is prone to various kinds of confounders (duration of use of the different COCs, intention of pregnancy, use for other reasons than contraception). In spite of these limitations, 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.

Bleeding pattern

The bleeding pattern of Seasonique was compared to the standard 21/7-day cycle regimen (Nordette, LGN 150 µg/ EE 30 µg and 7-day HFI) in the study PSE 302. 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 for the comparator 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.

Risk management plan

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

Overall benefit-risk balance

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. The CHMP was of the opinion that the benefit-risk balance of Seasonique and associated names is considered to be favourable

Grounds for positive opinion

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 has recommended the granting of the marketing authorisation(s) for which the summary of product characteristics, labelling and package leaflet remain as per the final versions achieved during the Coordination group procedure as mentioned in Annex III for Seasonique and associated names (see Annex I).