

Annex II

Scientific conclusions

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Perlinring 0.12mg/0.015mg/day is a vaginal delivery system containing etonogestrel and ethinylestradiol. The etonogestrel/ethinylestradiol combined contraceptive vaginal ring provides continuous delivery of contraceptive steroids through the vagina, avoiding the need for daily drug administration. Etonogestrel (ENG) is a 19-nortestosterone-derived progestagen and binds with high affinity to progesterone receptors in the target organs. Ethinylestradiol (EE) is an estrogen widely used in contraceptive products. The contraceptive effect of the vaginal delivery system is based on various mechanisms, the most important of which is the inhibition of ovulation.

ENG/EE ring is indicated for contraception and is intended for women of fertile age.

The recommended period of use of this product is 21 days; however, according to the summary of product characteristics (SmPC) of the reference medicinal product, even though not the recommended regimen, the contraceptive efficacy of the reference product is maintained for up to 28 days.

Bioequivalence of the proposed product to the reference medicinal product was demonstrated only for the period of 21 days, but not for 28 days. In order to address the concern of the extended (lengthened ring use) of up to 28 days, which is a deviation from the recommended use that is included in the SmPC of NuvaRing, the applicant provided further information on pharmaceutical quality data between the test and reference medicinal product, *in vitro* dissolution data which evaluated the rate of release of the test and reference product over 28 days, *In Vitro-In Vivo* Correlation (IVIVC) for the reference formulation for 28 days and an *In Vitro-In Vivo* Correlation (IVIVC) for the test formulation for 21 days, and the residual contents in the rings of etonogestrel and ethinylestradiol at 21 days for test and reference medicinal product.

The Pharmacokinetics Working Party (PKWP) and the Modelling and Simulation Working Party (MSWP) were also consulted during the CMDh procedure.

The reference Member State (RMS) United Kingdom, considered that, based on the totality of available data and in particular owing to the comparable pharmaceutical data, the similar residual content of EE and ENG, it is possible to conclude with a sufficient degree of certainty that bioequivalence of test and reference medicinal product is maintained over the period of 28 days.

However, the objecting CMSs (DE, NL and FR) contended that Perlinring 0.12mg/0.015mg per 24 hours vaginal delivery system is not approvable since the evidence for its use between day 21 and day 28 is built only on extrapolation, and bioequivalence in this period is considered not proven. The lack of *in vivo* data supporting the extended ring use (of up to 28 days), which is stated as a deviation from the recommended regimen (21 days) in line with information included in the product information of the reference medicinal product NuvaRing, was considered to be a potential serious risk to public health (PSRPH).

Day 60 of the CMDh procedure was on 2 August 2018. As no agreement could be reached during the CMDh procedure, a referral under Article 29(4) of Directive 2001/83/EC was triggered by the reference Member State United Kingdom (UK) on 7 August 2018.

Considering that the recommended posology of 21 days is supported by a bioequivalence study, the issue raised and discussed at the CHMP concerned the additional data submitted to support the use between day 21 and day 28 and whether these data were considered acceptable to support the extended use of up to 28 days (in line with the reference medicinal product).

The sampling period of 21 days in the conducted bioequivalence study is in line with the recommended use of the product, and it is undisputed that the evidence for bioequivalence of the test product Perlinring and the reference medicinal product NuvaRing has been adequately demonstrated for the recommended duration of use.

To address the issue of extended use up to 28 days, which is included in the SmPC of NuvaRing as a deviation to the recommended use, the applicant has additionally conducted IVIVC modelling to demonstrate that the behaviour of the ring does not change between 21 and 28 days, based on data from the test product for 21 days and from published data on reference product for 28 days. Although it is recognised that the model is not a surrogate for demonstrating bioequivalence (as *in vitro* data are generally not accepted to demonstrate bioequivalence), exceptions do exist such as in the case of BCS-based biowaiver. This modelling, together with the following information below was considered to provide further reassurance for the extended use up to 28 days:

- Pharmaceutical equivalence of test and reference medicinal product, and comparable *in vitro* dissolution data evaluating the rate of release of both over 28 days has been demonstrated
- There is also no risk of the active substances not being released over 28 days as there is an excess of active substances present in the ring. As mentioned above there is a significant residual amount of drug in both the test and the reference medicinal product at 21 days (residual content for test and reference products is approximately 87% vs. 86% for EE and for ENG 78% vs. 75% of the initial concentration remaining).
- Furthermore, the vaginal ring integrity is not expected to be affected if retained over the period of 28 days. Manual stress (in-process control) and tensile strength (finished product specification) are performed on the ring during manufacture and the ring is not expected to lose its integrity after 3 weeks of use. Additionally, the stability of the formulation has been shown to be maintained under extreme storage conditions with *in vitro* performance maintained.
- The tolerability of the ring after 28 days is also not expected to raise concerns given that the test and reference medicinal products have a similar polymer, active amounts and ring dimensions.

Overall summary of the scientific evaluation by the CHMP

In summary, scientific evidence supports that the generic product and reference medicinal product would behave similarly after Day 21 up to Day 28 of use. Therefore the CHMP agreed by majority, that the extended use of up to 28 days is supported by the totality of the data submitted by the applicant.

Grounds for the CHMP opinion

Whereas

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC,
- The Committee considered the totality of the data submitted by the applicant in relation to the objections raised as a potential serious risk to public health. The Committee considered the available data submitted in support of the use of Perlinring during an extended week up to 28 days, which included *in vivo-in vitro* correlation, pharmaceutical data such as *in vitro* dissolution and residual content, and ring integrity and tolerability.
- The Committee was of the view that the totality of data submitted justified the maintenance of the contraceptive efficacy up to 28 days for Perlinring, in line with the reference medicinal product NuvaRing.

The Committee, as a consequence, considers that the benefit-risk balance of Perlinring and associated names is favourable and therefore recommends the granting of the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains *as per* the final version achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.