18 October 2018
EMA/897708/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

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

Perlinring and associated names[1]

INN: etonogestrel/ethinylestradiol

Procedure number: EMEA/H/A-29(4)/1473

Note:

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

[1] Applicable when more than one invented name has been approved/applied for in the concerned member states

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

An application was submitted under the decentralised procedure (DCP) for Perlinring and associated names, 0.120mg/0.015mg per 24 hours vaginal delivery system on 16 May 2016.

The legal basis under which the application was submitted is: Article 10(1) of Directive 2001/83/EC (generic application). The reference product used for this generic application is "NuvaRing 0,120 mg/0,015 mg per 24 uur, hulpmiddel voor vaginaal gebruik".

The application was submitted to the reference Member State (RMS): UK and the concerned Member States (CMS): Austria, Belgium, Croatia, Czech Republic, Denmark, Estonia, Spain, Finland, France, Germany, Hungary, Iceland, Ireland, Italy, Lithuania, Latvia, The Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Slovakia and Sweden (Malta was withdrawn during clock stop).

The decentralised procedure UK/H/6234/001/DC started on 16 May 2016.

On day 210, major issues on the submitted data supporting the extended use of the product in the fourth week were raised by Germany, France and The Netherlands, and remained unresolved; hence the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh), under Article 29, paragraph 1 of Directive 2001/83/EC, by UK on 3 May 2018. The CMDh 60 day procedure was initiated on 4 June 2018.

Day 60 of the CMDh procedure was on 2 August 2018 and as no agreement could be reached the procedure was referred to the CHMP.

On 7 August 2018 the RMS UK therefore triggered a referral under Article 29(4) of Directive 2001/83/EC. Germany, France and The Netherlands raised objections concerning 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, and considered it to be a potential serious risk to public health (PSRPH).

2. Scientific discussion

2.1. Introduction

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 it is not the recommended regimen, the contraceptive efficacy of the reference product is maintained for up to 28 days.

The etonogestrel (ENG)/ethinylestradiol (EE) (Perlinring) 0.12/0.015mg/day vaginal delivery system developed by Actavis has demonstrated bioequivalence in Cmax, AUC0-t and AUC0-inf to the reference

medicinal product NuvaRing when tested over the period of intended use of 21 days, in an open labelled, randomised, single dose, two-way crossover study.

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:

- Pharmaceutical quality data between the test and reference medicinal product (concerning the composition, the release controlling mechanism, the dimensions of the ring, the manufacturing process, process validation methods and quality checks)
- *In vitro* dissolution data which evaluated the rate of release of the test and reference medicinal product over 28 days.
- An *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 were conducted.
- Residual contents in the rings of etonogestrel and ethinyelstradiol 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. In terms of the pharmacokinetic aspects, there was a split opinion in the PKWP on the acceptance of the proposed extrapolation. The PKWP concluded that although there is strong scientific support for continued release also for 21 to 28 days, it is not considered possible to prove that the test and reference products are bioequivalent during this period. The split views among the PKWP members are mainly related to different visions on the regulatory requirement in this case.

The MSWP considered that there is evidence, mainly from the deconvolution analysis, that the release rates are consistent, very similar to the fraction absorbed profiles and also very similar between the test and reference products, but the data are limited to 3 weeks for the test product. With regard to the integrated model for up to 4 weeks, the MSWP was of the view that the model did not adequately describe the interindividual variability and that the use of population pharmacokinetics methodology in this specific setting was of limited value.

The 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, FR, BE) 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.

2.2. Assessment of the issues raised as a potential serious risk to public health

Bioequivalence of the relevant pharmacokinetic (PK) metrics has been shown between Perlinring and NuvaRing when tested over the period of intended use of 21 days in an open labelled, randomised, single dose, two-way crossover study (ACT-15041). Equilibrium kinetics are achieved for both actives approximately one week after vaginal ring insertion, and the pharmacokinetic equivalence is observed within the study for two more weeks i.e. for a total of 21 days.

To address the issue of the extended use up to 28 days, the applicant has focused on the following scientific evidence:

Pharmaceutical data, in vitro dissolution and residual content

The test product (Perlinring) and reference medicinal product (NuvaRing) are pharmaceutically equivalent. They have the same composition (EE and ENG dissolved in an EVA copolymer core (28%) and surrounded by an EVA copolymer (9%) rate controlling skin) and release mechanism (diffusion).

In order to further support the claimed similarity and the expected safe and efficacious generic substitution during the period of extended use (from day 21 up to day 28), comparative *in vitro* dissolution data evaluating the rate of release of both products (test and reference batches used in the biostudy, n=12 replicates each) over 28 days were generated. Rate of *in vitro* release is similar over 28 days for both the test and reference products, independent of test conditions.

The applicant also argued that the maintained release up to 28 days is also supported by the large residual content of both drug substances in the vaginal rings which are far from being depleted after 3-week use. Indeed, after 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. There is therefore no risk of exhaustion of the active substances over 28 days.

In vitro – in vivo correlation

A two-stage (Level A IVIVc) deconvolution-based evaluation was performed by the applicant using an immediate release (intravenous) formulation described in the scientific literature, to preliminarily explore the *in vitro-in vivo* relationships. Notably, three test product batches manufactured at different sites as well as NuvaRing had very similar release rates and fell within the same Level A IVIVc supporting that the IVIV relationship is robust within the studied release rate, as expected from a rate controlling vaginal delivery system.

A one-stage differential equation-based approach utilising a traditional compartmental model framework was pursued in order to link *in vitro* release rates with the complete pharmacokinetic profile and to determine the extrapolation to 28 days.

An integrated direct IVIVc model was used to predict the expected *in vivo* behaviour of the test product based on the corresponding *in vitro* rates, maintaining the systemic pharmacokinetic model structure related to the active ingredients. The direct IVIVc model was thus externally qualified, as it was proven able to adequately describe the pharmacokinetic observations for the test product from the pivotal vaginal ring trial for both analytes, when using its specific input rate. Direct IVIVc model predictions driven by the test and reference products *in vitro* release data, were shown to be aligned with observations at 21 days (pivotal vaginal ring trial for both Test and Reference products), as well as with literature data for NuvaRing at 21 and 28 days. Thus the applicant confirms the suitability and predictive capacity of the developed model.

Plasma/serum levels after 28 days

Plasma concentrations of both ENG and EE during the extended 28-day period of use are predicted to be similar for the test and reference products, while during the 21-day period bioequivalence has been proven. Consequently, the applicant argues that it seems logical to conclude that the test product will show adequate contraceptive exposures after 28-day administration similar to the reference product. Furthermore, as confirmed by the large residual content after 21 days, it is unlikely that the active substances would be exhausted over the extended period (28 days).

Existing data suggest that serum levels of ENG above 90 pg/ml are necessary to effectively prevent ovulation (Ali *et al.*, 2017[2]; McNicholas *et al*.[3], 2017; Hohmann, 2009[4]; Díaz *et al*., 1991[5]). This is consistent with other publications reporting therapeutic serum levels of EE and ENG among women with normal and obese Body Mass Index (BMI) using a single contraceptive vaginal ring (CVR) for 6 weeks so that women who forget to remove the CVR at day 21 may well have continued contraceptive protection during the next 3 weeks.

3. Benefit-risk balance

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 open 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.

[2] Ali, M. et al., 'Extended Effectiveness of the Etonogestrel-Releasing Contraceptive Implant and the 20 mg Levonorgestrel-Releasing Intrauterine System for 2 Years Beyond U.S. Food and Drug Administration Product Labeling', Global Health: Science and Practice, Vol. 5 (4), December 2017, p.534-539.
[3] McNicholas C. et al., 'Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food and Drug Administration -approved duration', American Journal of Obstetrics and Gynecology, June 2017, p.586.e1-e6.
[4] Hohmann H., 'Examining the efficacy, safety and patient acceptability of the etonogestrel implantable contraceptive', Patient Preference and Adherence, July 2009, p.205-11.
[5] Díaz S. et al., 'Clinical trial with 3-keto-desogestrel subdermal implants', Contraception, Vol. 44(4), October 1991, p.393-408.

- 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.

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.

4. Grounds for 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.

Appendix 1

Divergent positions

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

Procedure No: EMEA/H/A-29(4)/1473

Perlinring and associated names

Divergent statement

The following CHMP Members consider that granting of the Marketing Authorisation of Perlinring and associated names is not favourable based on the following grounds:

Based on the *t*otality of data submitted, we are of the following opinion:

The posology of the reference product in this generic application, ie. Nuvaring, recommends a 21-day use of each ring but also provides the possibility of an extended use of 28 days with adequately maintained contraceptive efficacy.

Since Perlinring is a generic of Nuvaring according to Article 10(1) of Directive 2001/83/EC, as amended, and the possibility of an extended 28-day use is relevant for women, demonstration of bioequivalence up to day 28 is considered necessary. Although the quality and dissolution data of test and reference product and the residual drug content in the rings after removal at 21 days were shown to be similar, a 28-day *in vivo* bioequivalence cannot be waived because it cannot be confirmed that *in vivo* release characteristics of test and reference are similar for the whole period of 28 days. The Perlinring IVIVC model only covers 21 days and is not validated for 28 days and therefore the currently submitted 28 day dissolution data cannot be used to predict the *in vivo* release up to 28 days.

In conclusion, since bioequivalence between Perlinring and the reference product Nuvaring has not been established up to day 28, there is remaining uncertainty whether the contraceptive effect of Perlinring is adequate with extended use.

CHMP Members expressing a divergent opinion:

- Agnes Gyurasics (HU)
- Alexandre Moreau (FR)
- Andrea Laslop (AT)
- Bart Van Der Schueren (BE)
- Concepcion Prieto Yerro (ES)
- Daniela Melchiorri (IT)
- Ewa Balkowiec Iskra (PL)
- Jacqueline Genoux-Hames (LU)
- Johann Lodewijk Hillege (NL)
- Martina Weise (DE)
- Mila Vlaskovska (BG)
- Rajko Kenda (SL)
- Simona Badoi (RO)
- Jan Mueller-Berghaus (Co-opted Member)
- Koenraad Norga (Co-opted Member)