Annex II

Scientific conclusions

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On 17 September 2014, Gedeon Richter Plc submitted an application for Levonelle and associated names through a mutual recognition procedure (MRP) type II variation (UK/H/0803/001/II/022) with the United Kingdom acting as a Reference Member State (RMS). The Concerned Member States (CMS) were: Austria, Belgium, Czech Republic, Germany, Greece, Spain, France, Ireland, Iceland, Italy, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal and Sweden.

The applied variation was to add efavirenz to the list of medicines interacting with levonorgestrel (LNG) to the summary of product characteristics (SmPC) and package leaflet (PL) for Levonelle 1500 microgram (mcg) tablets.

The type II variation started on 17 September 2014. All Member States (MSs) supported the existence of a clinically relevant interaction however a few remained unsure about the advice on how to manage the interaction. Therefore the procedure was referred to the Coordination Group for Mutual Recognition and Decentralised Procedures – human (CMDh), under Article 13(1), paragraph 1 of Regulation EC No 1234/2008 by UK on 17 June 2015. The CMDh 60 day procedure was initiated on 3 August 2015. Day 60 of the CMDh procedure was on 1 October 2015, when a final position was reached by most MSs except Italy (IT). As no agreement could be reached, the procedure was referred to the CHMP.

On 1 October 2015, the United Kingdom (UK) as RMS triggered a referral under Article 13(2) of the Commission Regulation (EC) No 1234/2008. The CHMP was requested to give its opinion on whether a double dose of LNG 1500 mcg would be a suitable form of emergency contraception for patients taking concomitant hepatic enzyme inducers after unprotected intercourse or failure of a contraceptive method, in particular women who are unwilling or unable to use non-hormonal methods, such as a copper-based intra-uterine device (Cu IUD).

The scope of this procedure is limited to Levonelle and associated names which are authorised in the European Union (EU) as emergency hormonal contraceptives (EHC). Levonelle 1500mcg and associated names consists of a single tablet.

Overall summary of the scientific evaluation by the CHMP

The CHMP reviewed all data available from clinical studies, published literature, post-marketing experience, including responses submitted by the MAH in writing, as well as the results of a written consultation with patients and consumers, and healthcare professionals across the EU. A relevant summary of the conclusions is presented below.

(i) Reduction in plasma levels with efavirenz and other enzyme inducers

The study of Carten et al. (2012)[1], used a cross-over design, a clinically relevant dose of efavirenz and the size was reasonable for a drug-drug interaction (DDI) study. Despite some variabilities overall, the data show consistent and marked reduction by about half of the plasma LNG levels during concomitant administration of efavirenz, with decreases in LNG AUC_{0-12} of >40% observed in 90% of the women. In addition, plasma LNG levels were lower by a similar magnitude when LNG was administered via contraceptive implants in efavirenz users compared to HIV-positive women not yet in need of anti-retroviral therapy. Taken together, this suggests that the magnitude of the efavirenz effect has been reliably estimated[1].

[1] Carten ML, Kiser JJ, Kwara A, Mawhinney S, Cu-Uvin S. (2012) Pharmacokinetic Interactions between the Hormonal Emergency Contraception, Levonorgestrel (Plan B), and Efavirenz. Infectious Diseases in Obstetrics and Gynecology, 2012:137192, 4 pages

The relevance of the divided dosing used in the study[1] for the currently licensed single dose LNG was raised. Limited data with a 6mg dose of LNG shows higher Cmax than seen with 1.5mg, suggesting that saturation of LNG uptake does not occur at the standard EHC dose. Secondly, AUC, the main measure of exposure, has generally been found[2] to be dose-proportional. Finally, the dosing regimen used[1] was the previously approved posology for Levonelle, which was amended to a single 1500mcg dose following demonstration that the $AUC_{0-\infty}$ resulted in identical exposure and that there were no differences between the effectiveness or safety of LNG 2 x 750 mcg tablets (12 hour interval) and LNG 1500 mcg tablet administered as a single dose.

Therefore the CHMP is of the opinion that the findings of the above mentioned study[1] should apply equally to LNG EHC when it is taken as a single 1500mcg dose.

Specific data for interactions of other enzyme-inducers with EHC doses of LNG are not currently available. However studies following after 14 days treatment with St John's wort found similar >50% decreases in AUC for midazolam or alprazolam used as probes for CYP 3A4 activity. Also, decreases in exposure of the LNG component of combined hormonal contraceptives have been noted with several enzyme inducers: LNG AUC was reduced by 36 to 47% reductions with oxcarbazepine; 40 to 46% with carbamazepine; 42% with phenytoin; 37% with eslicarbazepine; and 40% with perampanel.

(ii) Clinical significance of reduced plasma LNG levels

The CHMP acknowledged the limited clinical data regarding lack of efficacy of LNG-containing contraceptives with concomitant use of CYP 3A4 enzyme inducers by which to judge the clinical significance of reduced plasma LNG levels during EHC.

There are also limited data on whether lower levels of LNG may be effective for EHC. One small study (n=58 women using cross-over design) found comparable efficacy of 750 and 1500mcg LNG using disruption of ovulation as an endpoint[3] when LNG was taken in the follicular phase, i.e. prior to ovulation.

Two parallel group studies examined contraceptive efficacy with lower doses of LNG: one study with 361 women observed similar crude pregnancy rates when LNG tablets were taken 8 hours after unprotected sexual intercourse (UPSI) using two formulations of 750mcg LNG tablets which were not bioequivalent. A second study looked at the contraceptive efficacy of LNG doses up to 400mcg, taken 3hours after UPSI by 4631 women in total. Exposure to 400mcg LNG represented the largest group, with 2801 patients studied, 71% for >6 months and 48% for > 12 months. There were 75 pregnancies in the 400mcg LNG treated group, yielding a failure rate of 3.52% and a method failure rate of 1.69%. The currently licensed dose of 1500mcg was not included in either of the contraceptive efficacy studies, so direct comparison of efficacy is not possible. Notably both contraceptive efficacy studies mentioned here required or allowed repeat use of LNG during the cycle and these studies examined contraceptive efficacy when LNG was used within 3 or 8 hours after UPSI and not when it used according to the current regimen, that is, within 72 hours of UPSI. This is important as contraceptive efficacy of LNG EHC diminishes with time since UPSI: from 95% within 24 hours to 58% if started between 48 and 72 hours. Currently the minimally effective dose for LNG EHC is not known.

Moreover, when other forms of LNG-containing contraception are considered, a consistent pattern emerges of reduced contraceptive control being seen, either in terms of breakthrough bleeding or ovulation, or pregnancies noted with reduced plasma LNG levels during concomitant use of enzyme

[2] Johansson E, Brache V, Alvarez F, Faundes A, Cochon L, Ranta S, Lovern M, Kumar N. (2002) Pharmacokinetic study of different dosing regimens of levonorgestrel for emergency contraception in healthy women. Hum Reprod.;17(6):1472-6.

[3] Croxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alvarez F, et al. (2004) Pituitary ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75-mg dose given on the days preceding ovulation. Contraception 70(6):442-50

inducers. Notably, there were 3 unintended pregnancies amongst efavirenz users in a 48 week study with LNG implants and the MAH has 6 post-marketing reports on their database of contraceptive failure with St John's wort, another enzyme inducer.

Although there are few adverse drug reaction (ADR) reports of contraceptive failure during concomitant use of enzyme inducers with LNG EHC, and none with efavirenz specifically, this is likely linked to significant under-reporting for loss of efficacy in general when expected contraceptive failure rates and widespread use of LNG EHC are considered. The reasons for the under-reporting are not known but may be due to an expectation of lower efficacy compared to other contraceptives.

For non-emergency forms of LNG-containing contraception, the decreased efficacy resulting from reduced plasma levels are considered to lead to in an increased risk of pregnancy. This is recognised in clinical guidance and in the product information of hormonal contraceptives which advise use of additional or alternative contraception.

The CHMP agreed that plasma exposure levels of LNG vary between women, but data from studies with combined hormonal contraceptives have indicated that plasma LNG levels are consistently reduced by concomitant use of liver enzyme inducers, mainly inducers of CYP3A4 enzymes. The recent study with LNG-containing emergency contraception[1] showed that concomitant administration of efavirenz reduces plasma levels of LNG (AUC) by around 50%. The minimally effective dose of LNG for emergency contraception has not been established, but it is important to preserve efficacy margins for contraception in users of enzyme inducers.

(iii) Management options – Dose increase / alternative treatment

Currently the SmPC and PL for Levonelle 1500mcg and associated names list a number of enzyme inducers which may affect contraceptive efficacy but do not provide any information on the magnitude of the effect or advice on appropriate management of the interaction, other than for the woman to tell her doctor. Specialist clinics are not necessarily aware of the importance of the interactions and women rely on specialist clinical advice. Therefore the CHMP recommended that clear SmPC advice on managing these interactions is needed for all potential EHC providers.

The SmPCs for regular contraception products containing LNG advise using additional or alternative methods of contraception, depending on the duration of use of the enzyme inducer.

It is accepted that a woman using an enzyme inducer would ideally use a method that is unaffected by the interaction; indeed such women would be unlikely to need EHC. However this may not be realistic in all situations. Currently two other forms of emergency contraception are available, ulipristal acetate and Cu-IUDs. The product information for ulipristal acetate advises to avoid use with concurrent enzyme inducers due to enhanced metabolism. Fitting a Cu-IUD is a skilled procedure and this option may not be available, suitable or acceptable for all women. Moreover, to access this, a woman needs first to be aware of the risks associated with medicines interacting with LNG. Thus the CHMP concluded that there is a need for timely and clear advice for clinically relevant interactions.

Part of this advice to women is for a dose adjustment to counteract reduced plasma LNG levels when EFV and the other enzyme inducing medicines are used. From the data available it was proposed the use of a double dose of LNG EHC during and for 4 weeks after cessation of treatment with any enzyme inducers currently listed in the SmPC for this product. On this basis a double dose of LNG EHC for EFV users and all other enzyme inducers is recommended. Cu-IUDs can be used up to 5 days following UPSI but this may not be an option for all women on medical grounds (e.g. following recent expulsion or perforation, recurrent vaginal infections, and increased risk of bleeding is undesirable for female HIV patients), due to access issues (lack of availability of appropriately skilled HCPs) or due to personal choice (e.g. for women not in long term relationships at the time of UPSI). Finally the decision on

whether a Cu-IUD is appropriate or not for a woman should be a clinical decision that considers her individual circumstances.

The CHMP considered the possibility that a double dose may not be adequate to fully compensate the effects of strong enzyme inducers. Although this possibility does exist, a double dose would still result in higher plasma LNG levels than under the current posology and thus reduce the risk of contraceptive failure. Interestingly, a recent publication of a small PK study[4] in obese women vs normal BMI women found that C_{max} and $AUC_{(0-2.5h)}$ of total LNG was doubled when a double dose of LNG EHC (3000mcg LNG) was used. Although this study was not in association with enzyme inducers, it suggests that linearity of C_{max} is maintained up to 3mg LNG.

Conversely, a double dose may over compensate the effects of less strong enzyme inducers. However in this case, the exposure to LNG would be less than that for a woman taking a double dose (i.e. 3 mg LNG) whilst not using a concomitant enzyme inducer. Non-clinical data, a prospective cohort study investigating human pregnancy outcomes after LNG EHC failure, and data from post-marketing reports of overdose all suggest that overdosing (on a one-off or occasional basis) does not cause severe adverse reactions and no new safety concerns were raised. Thus safety concerns related to the over compensation of less strong enzyme inducers would also seem unlikely.

In conclusion, the CHMP agreed that whilst the use of a Cu-IUD may be the preferred option for emergency contraception for use with all enzyme inducers, recommending a double dose of LNG EHC represents a pragmatic management option, with no significant known safety issues, to reduce the risk of contraceptive failure for women unable or unwilling to use a Cu-IUD. The SmPC and PL text amendments proposed address appropriately all concerns.

(iv) Communication to healthcare professional and patients on double dosing for EHC management

Concerns have been raised by the CHMP of potential for medication errors related to non-prescription supply (i.e. targeted patients not using the double dosing as unaware). There is a need to educate healthcare professionals and patients about the interaction concerns and the related recommendations. It is considered that specific training is not needed for healthcare professionals, rather a Dear healthcare professional communication (DHPC) should be issued to highlight the change in prescribing advice. In this respect, the CHMP recommended that the national competent authorities (NCAs) should outline the amendments to the SmPC and the reasons for the change through their normal means of communication with healthcare professionals.

In addition, the CHMP considered that instructions for an amended dose for users of enzyme inducers should be part of the package leaflet and should also be highlighted on the product outer carton labelling as the information should be available prior or during the purchase of the medicinal products to get the appropriate number of packs. In that regards, the CHMP recommended that to improve the delivery of the information, the effect of the enzyme inducers should be included directly after the usual dosage instructions on the same side of the carton.

In that way the CHMP wanted to ensure that the instructions on dosing are as clear as possible on the outer carton labelling and the package leaflet, in order to maintain the non-prescription supply without increasing the risk of medication errors. In order to assess the effectiveness and readability of this advice in the product information, a consultation was undertaken with patient and consumer groups and relevant healthcare professionals, with responses from across the EU. This showed that the majority of potential users could correctly identify from the information provided when it would be appropriate to use a single dose and when it would be appropriate to use a double dose, due to

[4] Edelman, A,B., Cherala, G., Blue, S.W., Erikson, D.W., Jensen, J.T., (2016) Impact of obesity on the pharmacokinetics of levonorgestrel-based emergency contraception: single and double dosing. Contraception, in press.

concomitant or recent use of interacting medicines or would seek advice from a healthcare professional. The responses also highlighted a low level of awareness of interactions with LNG EHC, underlining the need for proactive national communications on the outcome of the present review. For that reason the CHMP has discussed the key elements for communication to healthcare professionals and patients to facilitate the communication at national level.

In addition as the scientific conclusions of this assessment apply as well to the 750mcg LNG-containing medicinal products indicated in emergency contraception, the MAHs should take note of this recommendation and apply the scientific conclusions to those products accordingly.

To the extent that other 750mcg and 1500mcg LNG-containing medicinal products indicated in emergency contraception not included in this assessment but are currently authorised in the EU, or are subject to future authorisation procedures by the Member States, the CHMP recommends that the concerned member states take due consideration of these scientific conclusions.

Overall, the Committee concluded that the benefit-risk balance of Levonelle 1500mcg and associated medicinal products remains favourable, subject to the changes to the product information agreed.

Grounds for the CHMP opinion

Whereas,

- The Committee considered the referral under Article 13(2) of Regulation No 1234/2008.
- The Committee reviewed all available data from clinical studies, published literature, post-marketing experience, including responses submitted by the marketing authorisation holder (MAH), in support of the efficacy and the safety of Levonelle 1500mcg and associated names in relation to the interaction with efavirenz. Furthermore the Committee discussed data regarding other hepatic enzyme inducers including barbiturates and other medicines to treat epilepsy, medicines used to treat tuberculosis like rifampicin and herbal medicines containing Saint John's wort.
- The Committee took also into account written consultations of consumers, patients and healthcare professionals before recommending the agreed changes to the product information.
- The CHMP concluded that in view of the available data for Levonelle 1500mcg and associated names, information should be available on the effect of efavirenz and other hepatic enzyme inducers when taken concomitantly, or for 4 weeks after cessation of treatment with all enzyme inducers. In particular in order to manage the effect of this interaction, the amendments to the product information include the recommendation of double dose adjustment of Levonelle 1500mcg and associated names when a Cu-IUD is not suitable or available.

In view of the above, the Committee considers that the benefit-risk balance of Levonelle 1500mcg and associated names remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for Levonelle 1500mcg and associated names.