Direct Healthcare Professional Communication

01 December 2016

Levonorgestrel-containing emergency hormonal contraception: new advice for users of hepatic-enzyme inducers.

Dear Healthcare professional,

In agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA), the Marketing Authorisation Holders listed in table 1 of this letter would like to inform you of the following:

Summary

- Women seeking emergency contraception who have used enzyme-inducing medicine within the last 4 weeks, are advised to use a non-hormonal emergency contraceptive, i.e. a copper intrauterine device (Cu-IUD). If this is not an option, they should be advised to double the usual dose of levonorgestrel from 1.5mg to 3mg to compensate for the reduction in plasma levonorgestrel levels (see below).
- Exposure during pregnancy of some enzyme-inducing medicines has been associated with birth defects, so it is important to exclude pregnancy after use of levonorgestrel-containing emergency contraceptives (EC) listed below and provide advice on highly effective forms of regular contraception for women taking these medicines (see guidance from the Faculty of Sexual and Reproductive Health).
- The metabolism of levonorgestrel is known to be increased by concomitant use of liver enzyme inducers, mainly inducers of CYP3A4 enzymes. Recent evidence has shown that concomitant administration of the antiretroviral efavirenz (a medicine used to treat HIV) reduces plasma levels of levonorgestrel (AUC) by around 50%. Other hepatic enzyme-inducing medicines may produce similar reductions in plasma levels. This reduction in plasma levonorgestrel levels may reduce contraceptive efficacy of levonorgestrel-containing emergency hormonal contraceptives.
- No increased risk of side effects is expected from the higher dose for women who take a double dose of levonorgestrel EC under these circumstances. However, the specific combination of a double dose of levonorgestrel during concomitant use of an enzyme inducer has not been studied so users or healthcare professionals are reminded to report any side effects occurring with use of a double dose.
- Healthcare professionals are reminded that copper intrauterine devices (Cu-IUD) can be used as non-hormonal emergency contraception. As these are not affected by enzyme-inducing medicines, a Cu-IUD may be an appropriate alternative for some women, including those who use enzyme-inducing medicines or herbal products.

Background on the safety concern

Levonorgestrel-containing emergency contraceptives are taken as a single 1.5mg dose for emergency contraception within 72 hours after unprotected intercourse or failure of a contraceptive method. Efficacy is highest if it is taken soon after unprotected intercourse and diminishes with later use (from 95% within 24 hours to 58% if started between 48 and 72 hours).

Plasma exposure levels of levonorgestrel vary between women, but data from studies with combined hormonal contraceptives have indicated that plasma levonorgestrel levels are consistently reduced by concomitant use of liver enzyme inducers, mainly inducers of CYP3A4 enzymes. A recent study with levonorgestrel-containing emergency contraception (Carten *et al,* 2012) showed that concomitant administration of efavirenz reduces plasma levels of levonorgestrel (AUC) by around 50%.

The minimum effective dose of levonorgestrel for emergency contraception has not been established, but it is important to preserve efficacy margins for contraception in users of enzyme inducers.

The new advice for women seeking levonorgestrel emergency contraception and have used enzyme-inducing medicines or herbal medicines during the preceding 4 weeks is to use a non-hormonal EC, i.e. Cu-IUD. If this is not an option for her or if she is unable to see her doctor promptly, a doubling of the usual dose of levonorgestrel from 1.5mg to 3mg is recommended to compensate for the reduction in plasma levonorgestrel levels. The 4 week period represents the time required for CYP 3A4 enzymes to return to their normal levels after cessation of the enzyme-inducing medicine.

Exposure during pregnancy of some enzyme-inducing medicines has been associated with birth defects, so it is very important for women taking these medicines to exclude pregnancy after use of levonorgestrel EC even when a double dose is taken. Prescribers are also reminded of the importance of providing advice on reliable forms of regular contraception for women taking these medicines.

Copper intrauterine devices (Cu-IUD) are effective as non-hormonal emergency contraception and are not affected by enzyme-inducing medicines. A Cu-IUD may be fitted up to 5 days after unprotected intercourse and, if available, may be an appropriate alternative for some women, including women who use enzyme-inducing medicines or herbal products.

The information for prescribers and package leaflet is being revised to highlight the new dosing instructions for this category of women. The changes include information on the outer packaging to highlight when a doubling of the dose is recommended and clearer presentation of the relevant interacting medicines in the package leaflet.

No increased risk of side effects is expected from the higher dose for women who take a double dose of levonorgestrel EC under these circumstances. However, the specific combination of a double dose of levonorgestrel during concomitant use of an enzyme inducer has not been studied so users or healthcare professionals are reminded to report any side effects occurring with use of a double dose.

Healthcare professionals are reminded that levonorgestrel may inhibit cyclosporine metabolism and increase the risk of cyclosporin-induced side effects, so special consideration may be needed for women who take both cyclosporin and an enzyme-inducing medicine.

Medicines which affect Levonorgestrel levels

- Some medicines used to treat epilepsy (e.g. barbiturates, primidone, phenytoin or carbamazepine)
- Some medicines used to treat tuberculosis (e.g. rifampicin, rifabutin)
- Some medicines used to treat HIV (e.g. ritonavir, efavirenz)
- Some medicines used to treat fungal infections (e.g. griseofulvin)
- herbal remedies containing St John’s wort (Hypericum perforatum)

Call for reporting

Suspected adverse reactions should be reported to the HPRA using a Yellow Card obtained either from the HPRA, or electronically via the website at www.hpra.ie. Adverse reactions can also be reported to HPRA by calling (01) 676 4971.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates and product brand name.

Company contact point

Suspected adverse reactions should also be reported to the Marketing Authorisation Holder (see contact details below in table 1).

Table 1: Levonorgestrel containing emergency contraceptives licensed in Republic of Ireland:

Product Name	**PA Number**	**Market Authorisation Holder**	**Contact Details for medical enquiries**
Prevenelle 1500 microgram Tablet	PA0818/004/002	Medimpex UK Ltd	Consilient Health Ltd Block 2A Richview Office Park, Clonskeagh, Dublin 14, Ireland Telephone: +353 (0)1 2057760 Medical Information Direct Line: +353 (0)1 2057766 Medical Information e-mail: drugsafety@consilienthealth.com
Prevenelle 1500 microgram Tablet	PA1330/021/001	Gedeon Richter plc	Consilient Health Ltd Block 2A Richview Office Park, Clonskeagh, Dublin 14, Ireland Telephone: +353 (0)1 2057760 Medical Information Direct Line: +353 (0)1 2057766 Medical Information e-mail: drugsafety@consilienthealth.com
NorLevo 1.5mg Tablet	PA1166/002/001	Laboratoire HRA Pharma	Haines House 21 John Street Bloomsbury WC1N 2BF, UK Tel. : 1800 812 984 Email : med.info.ie@hra-pharma.com
Levonorgestrel Rowex	PA0711/267/001	Rowex Ltd	Newtown Bantry Co. Cork, Ireland Tel: +353 27 50077 Fax: +353 27 50417 contact details are as follows: pv@rowa-pharma.ie
Tyedra	PA1474/013/001	Laboratorio León Farma S.A	Avda. Miralcampo 7. Poligono Industrial Miralcampo. Azuqueca de Henares 19200 SPAIN Phone: +34 949 34 97 00 Pharmacovigilance@chemogroup.com

Annexes *(if applicable)*

The link below will connect with the area on the EMA's website, which provides further information on this issue.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Levonelle_1500_microgram_tablets_and_associated_names/human_referral_000405.jsp&mid=WC0b01ac05805c516f

References:

Carten ML, *et al*, (2012) Pharmacokinetic Interactions between the Hormonal Emergency Contraception, Levonorgestrel (Plan B), and Efavirenz. *Infectious Diseases in Obstetrics and Gynecology*, article ID:137192

Signature:

Signed on behalf of all Marketing Authorisation Holders included in table 1

Dr Kriszta Zolnay

Managing Director, Gedeon Richter UK Ltd