

Direct Healthcare Professional Communication

14 September 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 Medicines and Healthcare products Regulatory Agency, the Marketing Authorisation Holders listed in table 2 of this letter would like to inform you of the following:

Summary

- Women seeking emergency contraception (EC) who have used an 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 listed below and advise women to seek prompt medical advice if they do become pregnant. It is also important to provide advice on highly effective forms of regular contraception for women taking these medicines (see [guidance from the Faculty of Sexual and Reproductive Health](https://www.fsrh.org/documents/ceu-guidance-drug-interactions-with-hormonal-contraception-jan/). <https://www.fsrh.org/documents/ceu-guidance-drug-interactions-with-hormonal-contraception-jan/>)
- 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 (see list below). A recent study with levonorgestrel-containing emergency contraception (¹Carten *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 advice for women seeking levonorgestrel emergency contraception and who 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 and seek prompt medical advice if they do become pregnant. 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 key elements of the advice are included in the accompanying document, which you may find useful when advising patients.

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 EC 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*)

¹Carten 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*

Further Information

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

Call for reporting

Please continue to report any suspected adverse drug reactions to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme:

Website: www.mhra.gov.uk/yellowcard

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 can also be reported to the relevant Marketing Authorisation Holder (see contact details in table 1).


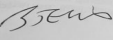

Table 1: Levonorgestrel containing emergency contraceptives licensed in the UK:
(not all products may be marketed)

Product Name	PL Number	Marketing Authorisation Holder	Contact details for Medical Enquiries
Levonelle One Step 1500 microgram tablet	PL 05276/0020	Medimpex UK Ltd	Bayer plc, Medical Information Department 01635 563116 medical.information@bayer.co.uk
Levonelle 1500 microgram Tablet	PL 05276/0019		Boots UK Medical Services 0115 9595165 drugsafety@boots.co.uk
Levonelle-2 750 microgram Tablet	PL 05276/0016		
Boots Emergency Contraceptive 1.5mg Tablet	PL 05276/0020		
Upostelle 1500 microgram tablet	PL 04854/0106	Gedeon Richter Plc	Consilient Health Ltd 0203 7511888 drugsafety@consilienthealth.com
Emergency Contraceptive Consilient 1500 microgram tablet	PL 04854/0105		
Levonorgestrel 1.5 mg tablet	PL 04854/0136	Gedeon Richter Plc	0207 6048806 medinfo.uk@gedeonrichter.eu
Emerres Una 1.5 mg tablet	PL 20117/0137	Morningside Healthcare Ltd	0116 2045950 medicalenquiry@Morningsidehealthcare.com
Emerres 1.5 mg tablet	PL 20117/0138		
Levonorgestrel 1.5mg Tablets	PL 35507/0123 PL 35507/0126	Lupin (Europe) Ltd	01565 751378 drugsafetyeurope@lupin.com
Ezinelle 1.5 mg tablet	PL 04569/1486	Generics UK Ltd	01707 853000 info.uk@mylan.co.uk
Levonorgestrel 1.5 mg	PL 04569/1374		
Isteranda 1.5mg tablet	PL 04416/1366	Sandoz UK Ltd	01276 698020 sandoz@professionalinformation.co.uk
Melkine 1.5 mg tablet	PL 34518/0020	Laboratorios Leon Farma SA	Laboratorios Leon Farma pharmacovigilance@chemogroup.net
Toomee 1.5 mg tablet	PL 00289/1763	Teva UK Limited	Teva UK Medical Information 0207 5407117 Medinfo@tevauk.com

Product Name	PL Number	Authorisation Holder Company Name	Phone Number
Levonelle One Step tablet 1500 micrograms	PL 10380/1404	Swinghope Ltd	020 8664 5988
Levonelle One Step tablet 1500 micrograms	PL 10383/1878	Primecrown Ltd	020 8839 3000
Levonelle One Step tablet 1500 micrograms	PL 10383/2025		
Levonelle One Step 1500 mcg tablets	PL 15184/1177	Lexon (UK) Ltd	01527 501900
Levonelle One Step 1500 mcg tablets	PL 15184/1280		
Levonelle One Step tablet 1500 mcg	PL 15814/0933	OPD Laboratories Ltd	0800 358 4427
Levonelle One Step tablet 1500 mcg	PL 15814/1182		
Levonelle One Step tablet 1500 mcg	PL 15814/1183		
Levonelle tablets 1500 mcg	PL 18799/2089	B and S Healthcare	0117 953 3455
Levonelle tablets 1500 mcg	PL 18799/2250		
Levonelle One Step tablet 1.5 mg	PL 18799/2319		
Levonelle One Step tablets 1500 mcg	PL 19488/1319	S and M Medical Ltd	020 8799 7600
Levonelle One Step tablet 1500 mcg	PL 19488/1663		
Levonelle tablets 1500 mcg	PL 20636/2631	Star Pharmaceuticals Ltd	020 8423 3800
Levonelle One Step tablet 1500 mcg	PL 21828/0335	Landmark Pharma Ltd	01302 365000
Levonelle One Step tablet 1500 mcg	PL 21828/0534		
Levonelle One Step 1500 mcg tablets	PL 30900/2385	Tenolol Ltd	020 8423 3800
Levonelle One Step tablet 1500 mcg	PL 33532/0384	MPT Pharma Ltd	01477 549310
Levonelle One Step tablets 1500 microgram	PL 39352/0240	Kosei Pharma UK Ltd	01753 515050
Levonelle One Step tablets 1500 microgram	PL 39352/0335		

This information is being provided jointly by the MAHs listed in the table below.

Table 2: Signatures

Marketing Authorisation Holder	Name	Signature
Medimpex UK Ltd	Dr Kriszta Zolnay, Managing Director	
Gedeon Richter plc	György Nemeth, MD, PhD, Chief Medical Officer	
Morningside Healthcare Ltd	Danesh Gadhia, Director	
Lupin (Europe) Ltd	Ben Ellis, General Manager – UK	
Generics/Mylan UK Ltd	Mr Balwant Heer, Global Head Product Safety & Risk Management & EU QPPV	
Sandoz UK Ltd	Dr Chris Goode, Medical Director	
Laboratorios Leon Farma SA	Dr Jaime Algorta, Medical Director & QPPV	
Teva UK Limited	Dr Ewan Walters, Medical Director UK & Ireland	