Levonorgestrel-containing emergency hormonal contraception: advice on interactions with hepatic enzyme inducers and contraceptive efficacy

Posaconazole (Noxafil): tablets and oral suspension are not directly interchangeable

Idelalisib (Zydelig▼): updated indications and advice on minimising the risk of infection

Letters sent to healthcare professionals in August 2016

Medicines or herbal remedies that induce cytochrome P450 3A4 enzymes reduce blood levels of levonorgestrel, which may affect emergency contraceptive efficacy. Women seeking emergency contraception who have used CYP3A4 enzyme inducers within the last 4 weeks, should preferably use a non-hormonal emergency contraceptive—ie, a copper intrauterine device. If this is not an option, these women should take double the usual dose of levonorgestrel; increasing from 1.5 milligrams to 3 milligrams (ie, 2 packs—see page 2).

We have received reports of medication errors with the antifungal posaconazole, related to substitutions of tablets and oral suspension at the same dose. These dose forms are not directly interchangeable: switching from posaconazole oral solution to tablets has resulted in cases of dose-related toxicity; whereas switching from tablets to oral solution has resulted in underdosing and lack of efficacy (see page 5).

Also this month, we have updated advice for idelalisib, after the conclusion of a review of safety, including the risk of infection (page 6).

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Levonorgestrel-containing emergency hormonal contraception: advice on interactions with hepatic enzyme inducers and contraceptive efficacy

Summary
Medicines or herbal remedies that induce CYP3A4 enzymes reduce blood levels of levonorgestrel, which may reduce emergency contraceptive efficacy.

Updated advice for healthcare professionals:

- Women seeking emergency contraception who have used cytochrome P450 3A4 (CYP3A4) enzyme inducers (see below) within the last 4 weeks, should:
  - preferably use a non-hormonal emergency contraceptive—ie, a copper intrauterine device
  - if this is not an option, double the usual dose of levonorgestrel from 1.5 milligrams to 3 milligrams (ie, 2 packs)

- For these women:
  - provide advice on highly effective ongoing contraception that is not affected by hepatic enzyme-inducing drugs (see guidance from the Faculty of Sexual and Reproductive Health)
  - advise them to have a pregnancy test to exclude pregnancy after use of levonorgestrel-containing emergency contraception
  - advise them to seek prompt medical advice if they do become pregnant

This updated advice is in line with existing guidance from UK experts in sexual and reproductive health, and applies to both prescription and non-prescription supply which will help ensure that women receive consistent advice. Product information for healthcare professionals and women and the outer packaging for levonorgestrel emergency contraception are being updated with this advice.

Levonorgestrel emergency contraception

**Indication and posology**

Levonorgestrel-containing emergency contraception is used to prevent unintended pregnancy when taken within 72 hours (3 days) of unprotected intercourse or failure of a contraceptive method. The sooner it is taken after having unprotected sex, the more effective it will be.

Levonorgestrel-containing emergency contraception is available with or without a prescription as a single 1500 microgram tablet, or on prescription as two 750 microgram tablets taken as a single dose.

**Effect of hepatic enzyme inducers on levonorgestrel metabolism**

Concomitant use of liver enzyme inducers—mainly inducers of CYP3A4 enzymes—increases the metabolism of levonorgestrel.
Concomitant administration of the antiretroviral efavirenz (used to treat HIV) reduces plasma levels (AUC) of levonorgestrel by around 50%. Data are not available for all CYP3A4 enzyme inducers; however, studies of levonorgestrel-containing combined hormonal contraceptives show that other hepatic enzyme-inducing medicines or herbal medicines may produce similar reductions in plasma levels. These contraceptive products already contain advice on additional or alternative methods of contraception.

Elevated levels of CYP3A4 enzymes can persist for up to 4 weeks after cessation of the enzyme-inducing medicine.

This decrease in plasma levonorgestrel may reduce contraceptive efficacy of levonorgestrel-containing emergency hormonal contraceptives.

**Examples of enzyme inducers that reduce plasma levonorgestrel levels**

Some medicines used to treat:

- epilepsy (eg, barbiturates, primidone, phenytoin, carbamazepine)
- tuberculosis (eg, rifampicin, rifabutin)
- HIV (eg, ritonavir, efavirenz)
- fungal infections (eg, griseofulvin)

Herbal remedies that contain St John’s wort (*Hypericum perforatum*) also reduce levonorgestrel levels.

See the [British National Formulary](#) for further examples of relevant interactions. The [University of Liverpool HIV Drug Interaction Checker](#) also provides useful drug interaction charts.

**Levonorgestrel dose as emergency contraception in current or recent users of hepatic enzyme inducers**

For women unable or unwilling to use a copper intrauterine device, a woman seeking emergency contraception who has used a hepatic enzyme inducer in the past 4 weeks, should double the usual dose of levonorgestrel (from 1.5 milligrams to 3 milligrams, 2 packs) to compensate for the reduced plasma levonorgestrel levels. Other instructions for use are the same as for the usual dose.

No increased risk of side effects is expected from the higher dose in these circumstances. Users and healthcare professionals are reminded to report any suspected side effects occurring with levonorgestrel, including any thought to be associated with a double dose of emergency contraception, on a [Yellow Card](#).

**Enzyme-inducing medicines: exposure during pregnancy**

Exposure during pregnancy to some of the enzyme-inducing medicines listed above has been associated with an increased risk of birth defects (see the summary of product characteristics for the specific medicine for more
information). It is therefore important to provide advice on highly effective forms of regular contraception for women who take these medicines, and to exclude pregnancy after use of levonorgestrel-containing emergency contraception.

**Information sheet for women**

The key elements of this advice are included in an information sheet for women, which you may find useful when advising them.

**Footnotes**

*Copper intrauterine devices*

These devices are effective as non-hormonal emergency contraception as well as providing reliable long-term contraception and are not affected by enzyme-inducing medicines. A copper intrauterine device may be fitted up to 5 days after unprotected intercourse and, if available, may be an appropriate method of emergency contraception for some women.

**Names of levonorgestrel-containing emergency contraception**

- Levonelle One Step 1500 microgram tablet
- Levonelle-2 750 microgram tablet (ie, for a double dose this is 4 tablets, 2 packs)
- Levonelle 1500 microgram tablet
- Levonorgestrel 1.5 mg tablet(s)
- Boots Emergency Contraceptive 1.5 mg tablet
- Emerres Una 1.5 mg tablet
- Emerres 1.5 mg tablet
- Ezinelle 1.5 mg tablet
- Isteranda 1.5 mg tablets
- Melkine 1.5 mg tablet
- Toomee 1.5 mg tablets
- Upostelle 1500 microgram tablets
- Emergency Contraceptive Consilient 1500 microgram tablet

**Ulipristal acetate**

Ulipristal acetate emergency contraception (EllaOne) is not recommended in women who are using enzyme-inducing drugs or who have stopped them in the last 4 weeks.
Further information

European Medicines Agency statement, May 2016

Faculty of Sexual and Reproductive Health guidance on drug interactions with hormonal contraceptives: advice on highly effective methods of contraception not affected by enzyme inducers

Faculty of Sexual and Reproductive Health guidance on emergency contraception


Posaconazole (Noxafil): tablets and oral suspension are not directly interchangeable

Summary
Switching from posaconazole oral solution to tablets has resulted in cases of dose-related toxicity, whereas switching from tablets to oral solution has resulted in underdosing and lack of efficacy.

Advice for healthcare professionals:
• posaconazole tablets and oral suspension are not directly interchangeable
• switching from oral suspension to tablets can lead to overdosing and serious adverse drug reactions, whereas switching from tablets to oral suspension can lead to underdosing and lack of efficacy
• prescribers should specify the dosage form for posaconazole on every prescription
• pharmacists should ensure that the correct oral form is dispensed to patients

Posaconazole (Noxafil) is a broad-spectrum triazole antifungal for the treatment and prevention of fungal infections.

Posaconazole is available as an oral suspension (40 mg/mL), tablets (100 mg), and concentrate for solution for infusion (300 mg).

Medication errors
In the UK, we are aware of 3 reports of medication errors related to substitutions of posaconazole tablets and oral suspension at the same dose.
Updated advice for healthcare professionals is available, after conclusion of a review of the safety of idelalisib, including the risk of infection.

Indications for idelalisib (Zydelig▼)

Chronic lymphocytic leukaemia (CLL):
- combined with rituximab for adults with CLL as first-line treatment in the presence of 17p deletion or P53 mutation in patients who are ineligible for any other therapies (note that this is the updated indication)

Further information

Letter sent to healthcare professionals, July 2016


Two reports were patients prescribed posaconazole tablets but were dispensed the oral suspension; one patient developed an infection which may have been related to the underdose. The third patient was prescribed posaconazole oral suspension but was dispensed tablets, reporting headache and renal impairment.

Posaconazole tablets and oral suspension are not interchangeable because of differences between the two forms in dosing frequency, administration with food, and plasma drug levels achieved.

The labelled oral dosage of posaconazole is:
- tablet: 300 mg/day (after a loading dose on day 1 of 600 mg/day)
- oral suspension: 600–800 mg/day

Product information for posaconazole is being updated to clarify that the oral solution cannot be directly substituted for the oral tablet, or vice versa, at the same dose. The outer cartons of the oral forms have also been revised to better distinguish the tablets from the oral suspension, and to include a warning statement that the products should not be substituted for one another without adjustment of the dose.
idelalisib continues to be indicated in combination with rituximab for adults with CLL who have received at least one prior therapy

Follicular lymphoma:
idelalisib continues to be indicated as monotherapy for adults with follicular lymphoma that is refractory to two previous lines of treatment

**Measures to minimise risk of infection in all patients**

**Pneumocystis jirovecii pneumonia (updated):**
- all patients should receive prophylaxis for *P. jirovecii* pneumonia during treatment with idelalisib and for up to 2–6 months after stopping
- duration of post-treatment prophylaxis should be based on clinical judgment, taking into account the patient’s risk factors such as concomitant corticosteroid treatment and prolonged neutropenia

**Cytomegalovirus infection (updated):**
- regular clinical and laboratory monitoring for cytomegalovirus infection is recommended in patients who are seropositive at the start of treatment with idelalisib or who have other evidence of a history of infection with this virus
- patients with cytomegalovirus viraemia but without signs of infection should be carefully monitored
- for patients with evidence of viraemia and clinical signs of infection, consideration should be given to interrupting idelalisib. Treatment may be restarted if the infection has resolved and if the benefits of resuming are judged to outweigh the risks. If idelalisib treatment is restarted, preemptive cytomegalovirus therapy should be considered

**General advice about risk of infection (reminder):**
- patients should be informed about the risk of serious or fatal infections during treatment
- idelalisib should not be started in patients with any evidence of ongoing systemic bacterial, fungal, or viral infection
- patients should be monitored for respiratory signs and symptoms throughout treatment, and should be advised to promptly report new respiratory symptoms
- absolute neutrophil counts should be monitored in all patients at least every 2 weeks for the first 6 months of treatment, and then at least weekly while count is less than 1000 per mm$^3$. Treatment should be discontinued if absolute neutrophil count falls below 500 per mm$^3$. Treatment can be restarted at a lower dose (100 mg twice daily) when the count rises above 500 per mm$^3$
Results of safety review

In March 2016, an in-depth EU safety review of idelalisib, including serious infection associated with idelalisib, was initiated following a signal from clinical trials. Precautionary, temporary safety measures were implemented and communicated in May 2016. The safety review concluded in July 2016, and updates to treatment recommendations have been made as outlined above. The benefits of idelalisib outweigh the potential risks in all current indications.

Clinical trial signal of infection

3 phase III clinical trials showed a signal of increased serious infection and infection-related mortality associated with idelalisib. The trials were assessing the addition of idelalisib to standard therapy in first-line CLL, and to the treatment of relapsed indolent non-Hodgkin lymphoma (small lymphocytic lymphoma)—ie, outside its currently authorised drug combinations or indicated populations.

The full review has concluded that the study results do not impact on the authorised use of idelalisib. However, data for efficacy and safety are limited in treatment-naive patients with CLL who have a 17p deletion or P53 mutation, and therefore the indication for first-line treatment (combined with rituximab) has been updated to specify patients ineligible for any other therapies.

The risk of serious infection is relevant to all indications and therefore the measures outlined above should be implemented to help minimise this risk.

Reporting of suspected adverse reactions

Suspected adverse reactions should be reported to us on a Yellow Card.

Further information

Letter sent to healthcare professionals, August 2016

Article citation: Drug Safety Update volume 10 issue 2, September 2016: 3.

Letters sent to healthcare professionals in August 2016

In August 2016, a letter was sent to relevant healthcare professionals to inform them of the outcome of a review of the safety of idelalisib (Zydelig▼), including the risk of infection (see also above).