Drug Safety Update

Latest advice for medicines users

The monthly newsletter from the **Medicines and Healthcare products Regulatory Agency** and its independent advisor the **Commission on Human Medicines**

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Contents

The **Medicines and Healthcare products Regulatory Agency** is the government agency which is responsible for ensuring that medicines and medical devices work, and are acceptably safe.

The **Commission on Human Medicines** gives independent advice to ministers about the safety, quality, and efficacy of medicines. The Commission is supported in its work by Expert Advisory Groups that cover various therapeutic areas of medicine.

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This month we inform you that the weight-loss drug orlistat may theoretically reduce the absorption of antiretroviral HIV medicines. Initiate orlistat treatment only after careful consideration of the possible impact on efficacy of antiretroviral HIV medicines. People who take antiretroviral HIV medicines should consult their doctor before taking non-prescription 60 mg orlistat—see article A1.

We also remind you of the interaction between St John's wort and hormonal contraceptives, including implants. This interaction reduces the contraceptive effect and increases the risk of unplanned pregnancy and applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data—see article A2.

Claire Tilstone, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Orlistat: theoretical interaction with antiretroviral HIV medicines

Orlistat may theoretically reduce the absorption of antiretroviral HIV medicines. Initiate orlistat treatment only after careful consideration of the possible impact on efficacy of antiretroviral HIV medicines. People who take antiretroviral HIV medicines should consult their doctor before taking non-prescription 60 mg orlistat

Orlistat is indicated for weight loss in combination with a low-calorie, low-fat diet. It is available as 120 mg capsules under the brand name Xenical and as 60 mg capsules under the brand name alli. Xenical is only available with a prescription, whereas alli is available without a prescription under the supervision of a pharmacist.

Orlistat is a potent, specific, and long-acting inhibitor of gastrointestinal lipases which decreases the amount of fat absorbed from the diet.

On the basis of reports from literature[1,2] and data obtained after licensing, orlistat may theoretically reduce the absorption of antiretroviral HIV medicines. This may be due to retention of lipophilic medicines in the gastrointestinal tract or reduced gastrointestinal tract transit time. This interaction could negatively affect the efficacy of antiretroviral HIV medications. Reports have been received of suspected interactions between orlistat and efavirenz, and between orlistat and lopinavir. However, the theoretical interaction mechanism described above could also apply to other antiretroviral medicines.

1. de Truchis P et al. *AIDS* 2010; **24:** 1235–36.
2. Kent SJ. *AIDS Res Hum Retroviruses* 2012; **28:** 961–62.

Advice for healthcare professionals:

- Initiate orlistat treatment only after careful consideration of the possible impact on efficacy of antiretroviral HIV medicines
- Pharmacists should advise people who take antiretroviral HIV medicines to consult their doctor before taking alli in light of the possible interaction
- Suspected adverse reactions with orlistat, whether prescribed or obtained over the counter, should be reported to us on a Yellow Card (www.mhra.gov.uk/yellowcard)

Article citation: Drug Safety Update March 2014 vol 7, issue 8: A1.

A2 St John's wort: interaction with hormonal contraceptives, including implants—reduced contraceptive effect

St John's wort interacts with hormonal contraceptives. This interaction reduces the effectiveness of these contraceptives and increases the risk of unplanned pregnancy. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data

St John's wort (*Hypericum perforatum* L.) is a herbal medicine traditionally used to relieve slightly low mood and mild anxiety.

We have received two Yellow Card reports in the last quarter of 2013 of suspected interactions in women with implanted contraceptives containing etonogestrel (Nexplanon and Implanon). These women started taking St John's wort and then had unplanned pregnancies. A total of 19 reports of suspected interactions between St John's wort and hormonal contraceptives have been received through the Yellow Card scheme since 2000 (four for contraceptive implants and 15 for contraceptive pills). Of these suspected interactions, 15 cases resulted in unplanned pregnancies and the remaining four cases in association with contraceptive pills resulted in breakthrough bleeding without pregnancies.

Product information:
http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm

There are warnings about these interactions and their consequences in the product information provided with all contraceptives and the authorised St John's wort products. Some unlicensed products on the UK market or available online do not include the appropriate warnings regarding possible interactions. The lack of warnings does not mean these products do not interact with other products.

Further information:
Guidance for consumers: the THR certification mark:
http://www.mhra.gov.uk/home/groups/es-herbal/documents/websiteresources/con060025.pdf

Advise women who are using combined and progestogen-only hormonal contraceptives that herbal products containing St John's wort can decrease the effect of this contraceptive cover. Therefore, women taking hormonal contraception for pregnancy prevention should not take herbal products that contain St John's wort. This applies to all hormonal contraceptives except intrauterine devices, for which there are currently no data.

Advice for healthcare professionals:

- Advise women taking hormonal contraceptives for pregnancy prevention not to take herbal products containing St John's wort
- Encourage women to read the Patient Information Leaflet that comes with their hormonal contraceptive

Product information:
http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm

Article citation: Drug Safety Update March 2014 vol 7, issue 8: A2.

Stop press

S1 Strontium ranelate: cardiovascular risk—restricted indication and new monitoring requirements

The European Medicines Agency (EMA) has concluded its review of the risks and benefits of strontium ranelate (Protelos). The EMA considered that strontium ranelate should only be used by people for whom there are no other treatments for osteoporosis. The cardiovascular risks identified with strontium ranelate may be sufficiently reduced in this population by restricting its use to people without cardiovascular contraindications (as advised in April 2013—see below) and by monitoring cardiovascular risk regularly.

Advice for healthcare professionals:

- Strontium ranelate is now restricted to the treatment of severe osteoporosis in postmenopausal women and adult men at high risk of fracture who cannot use other osteoporosis treatments due to, for example, contraindications or intolerance
- Treatment should only be started by a physician with experience in the treatment of osteoporosis
- The risk of developing cardiovascular disease should be assessed before starting treatment. Treatment should not be started in people who have or have had:
    - ischaemic heart disease
    - peripheral arterial disease
    - cerebrovascular disease
    - uncontrolled hypertension
- Cardiovascular risk should be monitored every 6–12 months
- Treatment should be stopped if the individual develops ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease, or if hypertension is uncontrolled

Further information:
EMA statement:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Protelos_and_Osseor/human_referral_prac_000025.jsp&mid=WC0b01ac05805c516f

Article citation: Drug Safety Update March 2014 vol 7, issue 8: S1.

S2 **Methysergide: serious fibrotic reactions—restricted use and new monitoring requirements**

Methysergide (Deseril) should only be used for the prophylactic treatment of severe intractable migraine and episodic and chronic cluster headache in adults when treatment with standard medicines has failed. Treatment should be initiated and supervised by specialists.

A Europe-wide review concluded that there is a risk of fibrosis (mainly retroperitoneal fibrosis) associated with methysergide treatment. This side effect may be serious and in some cases irreversible or fatal. Healthcare professionals should note the following advice to help minimise the risks:

Advice for healthcare professionals:

- Methysergide should only be used for prophylaxis of:
  - severe intractable migraine (with or without aura) with functional disability in adults when treatment with standard medicines has failed. Previous treatment must have included medicines of other classes for at least 4 months at the maximum tolerated dose
  - episodic and chronic cluster headache in adults when treatment with standard medicines has failed. Previous treatment must have included medicines of at least two classes for at least 2 months each
- Methysergide should no longer be used to treat diarrhoea caused by carcinoid disease
- Methysergide should only be started and supervised by specialised physicians with experience in the treatment of migraine and cluster headache
- People should be screened for fibrosis at the start of treatment and at least every 6 months thereafter. Screening must include heart ultrasonography, abdominal MRI, and pulmonary function tests. Treatment must be discontinued if symptoms suggesting fibrosis occur unless an alternative cause is confirmed
- The continued need for methysergide treatment must be reassessed every 6 months using a treatment-free interval of at least 4 weeks between treatment courses

Availability in the UK
Although methysergide is authorised in the UK, this product was discontinued in April 2013 due to manufacturing problems. It is not clear when or if this product will return to the UK market.

We are aware of imports of unlicensed methysergide for a specific patient's needs. It is important to be aware that the product information supplied with these unlicensed products may not include all the relevant warnings. People who use unlicensed methysergide should be monitored as outlined above to minimise the risk of side effects.

DSU article on off-label or unlicensed use of medicines:
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087990

Further information
European Medicines Agency statement:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Methysergide-containing_medicines/human_referral_000363.jsp&mid=WC0b01ac05805c516f

Article citation: Drug Safety Update March 2014 vol 7, issue 8: S2.

Stop press

S3 **Dorzolamide hydrochloride/timolol maleate (Cosopt) preservative-free eye drops: new pipette design**

December 2013 Cosopt article: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON350696

Cosopt guidance: http://www.mhra.gov.uk/home/groups/comms-po/documents/news/con370021.pdf

In December 2013 we reported eye injuries caused by the pipette design of Cosopt preservative-free eye drops. Because of these injuries, a new pipette design was introduced in February 2014 as an interim measure. The instructions for using the new design are enclosed in the product packaging. The old pipette design is now being withdrawn. Please see further guidance on the MHRA website, including an updated Patient Information Leaflet and detailed instructions for use.

Article citation: Drug Safety Update March 2014 vol 7, issue 8: S3.

Other information from the MHRA

O1 **Combined hormonal contraceptives: risk of venous thromboembolism—clarification of advice**

February 2014 CHC article: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON377645

The February 2014 edition of Drug Safety Update included an article about combined hormonal contraceptives (CHCs) and risk of venous thromboembolism. This article refers to a letter that was sent to healthcare professionals through the Central Alerting System on Jan 22, 2014. Annexes 2–4 of the letter advise what contraception a woman should use instead of CHCs in the event of: major surgery; a period of prolonged immobilisation; or if she smokes and is older than 35 years.

CHC information on MHRA website: http://www.mhra.gov.uk/Safetyinformation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-G-L/Hormonalcontraceptives/Combinedhormonalcontraceptives/index.htm

The annexes recommend that a non-hormonal form of contraception should be used in these situations; however, they ought to have stated that a different form of contraception should be used. This clarified advice allows for use of progestogen-only contraception or non-hormonal contraception. Correct information is provided on the MHRA website.

Article citation: Drug Safety Update March 2014 vol 7, issue 8: O1.