Drug Safety Update

MHRA

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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In August 2010, we reported that the product information for saquinavir had recently been updated to reflect the results of a QT study in healthy volunteers. Saquinavir is contraindicated in patients at high risk of arrhythmia, and in patients using other medicines that may cause QT or PR prolongation. More recently, the potential clinical effect of these findings on the safe and effective use of saquinavir has been reviewed within Europe. As an additional precautionary measure, half the standard dose of saquinavir should be used for the first week of therapy: ie, 500 mg saquinavir plus 100mg ritonavir, twice daily. See article A1 for further information.

And as the year draws to a close, you can remind yourself about some of the important drug-safety topics featured in Drug Safety Update this year by completing our quiz.

Please do not send your answers to us, this quiz is just for fun!

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Drug safety advice

A1 Saquinavir: update on potential risk of arrhythmia—reduced dose for initial treatment

Further to recent concerns over the effect of saquinavir on QT and PR prolongation, antiretroviral-treatment-naïve patients should start saquinavir at a reduced dose for the first week of treatment

Saquinavir (Invirase) is a protease inhibitor indicated in combination with ritonavir and other antiretroviral drugs for treatment of HIV infection. The standard dose of saquinavir/ritonavir in adults and adolescents older than 16 years is 1000 mg/100 mg twice daily.

Previous advice for saquinavir

In August 2010, we reported that the product information for saquinavir had recently been updated to reflect the results of a QT study[1] in healthy volunteers. This study found that saquinavir had dose-dependent effects on the QT and PR interval that were greater than those seen with moxifloxacin, the active control drug.

As a result, saquinavir is contraindicated in patients at high risk of arrhythmia, and in patients using other medicines that may cause QT or PR prolongation, such as the other protease inhibitors atazanavir and lopinavir, and methadone. Baseline and follow-up electrocardiogram recording in patients taking concomitant drugs known to increase the plasma levels of saquinavir is also recommended (eg, potent inhibitors of the cytochrome p450 3A4 enzyme such as the protease inhibitor nelfinavir, the antifungal itraconazole, and proton pump inhibitors such as omeprazole).

More recently, the potential clinical effect of these findings on the safe and effective use of saquinavir has been reviewed within Europe. Despite the potentially proarrhythmic effects observed in the QT study, no signal of clinical events has been detected from post-licensing safety monitoring since saquinavir was authorised in 1996. However, an absence of case reports is not sufficient to exclude a risk in saquinavir-treated patients.

Treatment-naïve patients

Patients considered to be at the highest risk of QT and PR prolongation with saquinavir are those not previously exposed to any antiretroviral drugs (ie, treatment-naïve patients), with the greatest risk being in the first week of treatment.

On the basis of pharmacokinetic modelling, the European Medicines Agency's Committee for Medicinal Products for Human Use has recommended that, as an additional precautionary measure, half the standard dose of saquinavir should be used for the first week of therapy: ie, 500 mg saquinavir plus 100 mg ritonavir, twice daily. Pharmacokinetic modelling has shown that this lower dose will minimise QT prolongation during the period when patients are most at risk, while maintaining sufficient antiretroviral activity. The potential risk of arrhythmia in treatment-naïve patients receiving the reduced initial dose will be further investigated in a new study.

The benefits of saquinavir in the authorised indication continue to outweigh the risks.

Advice for healthcare professionals:

Cautions and monitoring

- Do not use saquinavir in patients with congenital or acquired QT prolongation, or

1 Anson BD, et al. Lancet 2005; **365**: 682–86.

Further information

Saquinavir: effects on QT and PR interval prolongation
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON090891

European Medicines Agency press release
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/10/WC500098345.pdf

Letter for healthcare professionals sent in July 2010
http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/con090791

other predisposing conditions for cardiac arrhythmias, including concurrent therapy with other drugs that prolong the QT and/or PR interval

- If possible, avoid use of saquinavir with drugs known to increase the plasma level of saquinavir. If no alternative treatment options are available, see below
- In all patients starting saquinavir, electrocardiography should be done before initiating treatment, and after approximately 3–4 days of therapy
- Do not use saquinavir in patients with a QT interval of >450 milliseconds
- Discontinue saquinavir if patients develop: QT prolongation of >480 milliseconds or >20 milliseconds from pretreatment measurement; PR prolongation; or arrhythmias
- Warn patients of the arrhythmogenic risk with saquinavir and the need to report any signs of cardiac arrhythmias to their physician (eg, chest palpitations, syncope, presyncope)

Dose recommendations

- In antiretroviral-treatment-naïve patients, use a reduced dose of saquinavir (ie, 500 mg plus 100 mg ritonavir, twice daily) for the first week of therapy
- Do not exceed the recommended dose of saquinavir because the magnitude of QT and PR prolongation is likely to increase with raised plasma levels of saquinavir

Article citation: Drug Safety Update Dec 2010 vol 4, issue 5: A1.

Quiz

H1 **End-of-year quiz: Test your drug-safety knowledge**

Do you read Drug Safety Update every month? Then test your knowledge of drug safety in our annual quiz.

If you participate in Continuing Professional Development/Continuing Medical Education, you may be able to use the completed quiz as evidence of learning through reading of Drug Safety Update. To claim personal CPD points in this way, we suggest you keep a copy of the quiz, together with your answers and the bulletin articles.

The answers are given overleaf.

An answer can be regarded as correct if one part of the whole question is answered correctly. Some articles in Drug Safety Update are more relevant for some healthcare professionals than for others, so feel free to attempt only the questions related to your specialty!

Please do not send your answers to us, this quiz is just for fun!

Q1. Current evidence indicates that the small risk of congenital cardiac defects associated with **fluoxetine** use in early pregnancy, when compared with paroxetine, is:

a) higher
b) approximately the same
c) lower

Q2. Which **antidiabetic drug** was suspended this year?

Q3. Use of which **proton pump inhibitors with clopidogrel** should be discouraged unless considered essential?

d) Esomeprazole
e) Lansoprazole
f) Omeprazole
g) Pantoprazole
h) Rabeprazole

Q4. Prescribers should consider the risk of persistent pulmonary hypertension in the newborn with which drugs during pregnancy (particularly the later stages), following recent epidemiological evidence?

Q5. In patients taking **valproic acid/sodium valproate**, concomitant use of which class of antibiotics is not recommended due to an interaction that may lead to inadequate seizure control? To manage this interaction, why was monitoring of sodium valproate levels or making dose adjustments not recommended?

Q6. For which patients only should high-dose (80 mg) **simvastatin** be considered?

Q7. **Quinine** is not a routine treatment for nocturnal leg cramps. When should it be considered?

Q8. The European Medicines Agency has recommended that the use of the wakefulness-promoting agent **modafinil** should be restricted to treat only which condition?

Q9. **Codeine-containing liquid over-the-counter medicines** should not be used to treat cough in those younger than age:

i) 5 years
j) 12 years
k) 18 years

Q10. In patients treated with **tamoxifen** for breast cancer, concomitant use of potent inhibitors of the CYP2D6 drug-metabolising enzyme may be associated with variability in clinical response. Therefore, use of drugs that are potent inhibitors of this enzyme should be avoided whenever possible in these patients. Give an example of one such potentially interacting drug.

Q11. A patient has attempted suicide; the suicidal act is thought to be associated with a medicine that has been used in the UK for many years. 'Suicidal ideation' is already listed as a recognised rare undesirable effect in the medicine's product information. Should you still report this suspected adverse drug reaction? If so, how should you report it?

Quiz answers

A1. b) approximately the same

Article citation: Drug Safety Update March 2010, vol 3 issue 8: 4.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON091089

A2. Rosiglitazone has been withdrawn from clinical use because of an increased cardiovascular risk.

Article citation: Drug Safety Update Oct 2010, vol 3 issue 3: S1.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096804

A3. a) Esomeprazole, c) Omeprazole

Article citation: Drug Safety Update April 2010, vol 3, issue 9: 4.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087711

A4. Epidemiological evidence suggests that SSRIs, selective serotonin reuptake inhibitors, may increase the risk. Furthermore, a potential risk for SNRIs, selective noradrenaline reuptake inhibitors, cannot be ruled out taking into account the related mechanisms of action.

Article citation: Drug Safety Update May 2010, vol 3 issue 10: 2.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085130

A5. Carbapenems: doripenem, ertapenem, imipenem with cilastatin, and meropenem. Given the large magnitude and rapid time course of this interaction, monitoring of sodium valproate levels or making dose adjustment are unlikely to manage this interaction.

Article citation: Drug Safety Update May 2010, vol 3 issue 10: 4.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085143

A6. 80 mg simvastatin should only be considered for patients with severe hypercholesterolaemia and high risk of cardiovascular complications who have not achieved their treatment goals on lower doses, when the benefits are expected to outweigh potential risks. Myopathy is a known side effect of all statins, and the risk increases with higher doses.

Article citation: Drug Safety Update May 2010, vol 3 issue 10: 7.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085169

A7. Quinine should only be considered when: cramps cause regular disruption of sleep; cramps are very painful or frequent; other treatable causes have been ruled out; and when non-pharmacological measures (eg, passive stretching exercises) have not worked.

Article citation: Drug Safety Update June 2010 vol 3 issue 11: 3.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON085085

A8. Sleepiness associated with narcolepsy. Modafinil should no longer be used for the treatment of excessive sleepiness associated with obstructive sleep apnoea or chronic shift work sleep disorder.

Article citation: Drug Safety Update Aug 2010 vol 4 issue 1: S1
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON090901

A9. d) 18 years

The Commission on Human Medicines and its Paediatric Medicines Expert Advisory Group have advised that codeine-containing over-the-counter liquid

medicines should notbe used for cough suppression in those younger than 18 years. Coughs and colds occur frequently in young children, but are self-limiting are rarely harmful if left untreated. Many medicines given to children have not been properly studied in this age-group. Specific paediatric studies are needed because of differences between adults and children in drug handling or drug effects, which may lead to different dose requirements.

Article citation: Drug Safety Update Oct 2010 vol 4 issue 3: H3.
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON096805

A10. Examples of potent CYP2D6 inhibitors include paroxetine, fluoxetine, bupropion, quinidine, and cinacalcet.

Article citation: Drug Safety Update Nov 2010 vol 4 issue 4: A1
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON099863

A11. Yes – serious suspected adverse drug reactions should be reported for all medicines and vaccines, including those that are considered to be well-established. If there are significant changes in the frequency or severity of adverse effects that are already listed, further regulatory action can be taken. You can report a reaction by filling in a Yellow Card, available online at www.yellowcard.gov.uk.

How did you score?

Score 8–11:
Excellent –Drug Safety Update expert

Score 5–7:
Very good

Score below 5:
Stay up to date: keep reading Drug Safety Update!

Article citation: Drug Safety Update Dec 2010 vol 4, issue 5: H1.

Stop press

S1 Fibrates: European Medicines Agency concludes first-line treatment is not recommended

The European Medicines Agency's Committee for Medicinal Products for Human Use has concluded that the benefits of the four fibrates—bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil—continue to outweigh the risks in the treatment of patients with blood-lipid disorders. However, healthcare professionals should not prescribe them to newly diagnosed patients as first-line treatment, except for those with severe hypertriglyceridaemia or those who cannot take statins.

Further information

Prescribing advice for fibrates can be found in the November 2007 issue of Drug Safety Update
http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON079321

European Medicines Agency press release
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/10/news_detail_001135.jsp&murl=menus/news_and_events/news_and_events.jsp&mid=WC0b01ac058004d5c1

National Prescribing Centre information on lipid management
http://www.npci.org.uk/therapeutics/cardio/cdlipids/workshops/workshop_60minute_elearn_event1.php

Article citation: Drug Safety Update Dec 2010 vol 4, issue 5: S1.