

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

Drug safety advice	Saquinavir: effects on QT and PR interval prolongation	A1
	Calcium gluconate injection in small-volume glass containers: new contraindications due to aluminium exposure risk	A2
Stop Press	Modafinil: European Medicines Agency recommends restricted use	S1
	Rosiglitazone: current advice on cardiovascular risk	S2
	Topical ketoprofen: reminder on risk of photosensitivity reactions	S3

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 light of recent studies of the effect of the HIV protease inhibitor saquinavir on cardiac conduction, this drug is now contraindicated in patients at high risk of arrhythmia, and in patients using other medicines that may cause QT or PR prolongation. Warnings over its use in patients at moderate risk of arrhythmia, together with recommendations for monitoring by electrocardiogram, have also been included in the product information. Further information to support safer use of saquinavir is provided in article A1.

We have become aware that aluminium can be leached from glass after contact with calcium gluconate solution, leading to a risk of exposure to aluminium. Accumulation of aluminium might have adverse effects on bone mineralisation and neurological development in children and those with renal impairment. Therefore, calcium gluconate injection sterilised in small-volume glass containers is now contraindicated for use as repeated or prolonged treatment, including as an intravenous infusion, in children younger than 18 years and in patients with renal impairment. To limit the exposure of patients to aluminium, especially in those with impaired renal function and in children, calcium gluconate injection in small-volume glass containers is also contraindicated in the preparation of total parenteral nutrition solutions. Use of calcium gluconate injection packed in plastic containers is recommended to reduce aluminium burden in vulnerable patients (see A2).

Also this month, see our important round-up of news from recent Europe-wide reviews to support safer use of the wakefulness-promoting agent modafinil, rosiglitazone for diabetes, and of topical ketoprofen for pain relief (S1 - S3).

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

Drug safety advice

A1 Saquinavir: effects on QT and PR interval prolongation

Saquinavir has a marked effect on QT and PR prolongation and is contraindicated in patients at high risk of cardiac arrhythmias, and in patients using other drugs that may cause QT and/or PR interval prolongation. Saquinavir should be discontinued if patients develop arrhythmias, QT prolongation, or PR prolongation

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.

HIV protease inhibitors and QT interval prolongation

In February 2005, a study^{c1} suggested that some protease inhibitors, including saquinavir, could predispose patients to QT interval prolongation and torsade de pointes. As a result, the effects of saquinavir on cardiac conduction were further investigated.

c1 Anson BD, et al. Lancet 2005; 365: 682–86

Saquinavir QT study

A thorough QT study assessed the effects of therapeutic (1000 mg/100 mg twice daily) and supratherapeutic (1500 mg/100 mg twice daily) doses of saquinavir/ritonavir on QT interval compared with placebo and the active control moxifloxacin. The study showed that the saquinavir/ritonavir groups had a prolonged QT interval, and that risk appeared greater than with moxifloxacin:

	Therapeutic saquinavir/ritonavir	Supratherapeutic saquinavir/ritonavir	Moxifloxacin active control	Placebo
Proportion with QTc 450– 480 milliseconds*	11%	18%	0%	0%
Proportion with PR prolongation >200 milliseconds	40%	47%	3%	5%

*No volunteers had QT prolongation >500 milliseconds or torsades de pointes.

Syncope

Cases of syncope or presyncope occurred at a higher than expected rate and were seen more frequently on treatment with saquinavir/ritonavir.

Outcome

In light of these findings, saquinavir is now contraindicated in patients at high risk of arrhythmia, and in patients using other medicines that may cause QT or PR prolongation. The table below shows examples of drugs contraindicated with saquinavir/ritonavir use due to potential for life-threatening arrhythmias:

Drug class	Drugs contraindicated with ritonavir boosted saquinavir
Protease inhibitors	Atazanavir/ritonavir, lopinavir/ritonavir
Narcotic analgesics	Methadone
Antiarrhythmics	Hydroquinidine, amiodarone, flecainide, dofetilide, sotalol
Tricyclic antidepressants	Amitriptyline, imipramine, trazodone
Anti-infectives	Clarithromycin, erythromycin
Antipsychotics	Clozapine, pimozide, haloperidol, sertindole, phenothiazines
Antihistamines	Terfenadine, astemizole and mizolastine
Phosphodiesterase type-5 inhibitors	Sildenafil, vardenafil, tadalafil

The use of other drugs that increase plasma levels of saquinavir, such as potent inhibitors of the cytochrome p450 3A4 enzyme, is not recommended (eg, the protease inhibitor nelfinavir, the antifungal itraconazole, and proton pump inhibitors such as omeprazole). Warnings over the use of saquinavir in patients at moderate risk of arrhythmia, together with recommendations for monitoring by electrocardiogram, have also been included in the product information. The arrhythmogenic potential of saquinavir remains under close review.

Advice for healthcare professionals:

- Do not use saquinavir in patients with congenital or acquired QT prolongation or other predisposing conditions for cardiac arrhythmias, including concurrent therapy with other drugs that prolong the QT and/or PR interval
- Avoid use of saquinavir with drugs known to increase the plasma level of saquinavir, unless no alternative treatment options are available
- Do not exceed the recommended dose of saquinavir because the magnitude of QT and PR prolongation may increase with raised plasma levels of saquinavir
- Consider baseline and follow-up electrocardiogram recording (eg, in patients taking concomitant drugs known to increase the plasma level of saquinavir)
- Discontinue saquinavir if patients develop arrhythmias, QT prolongation, or PR prolongation
- 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)

Further information

European Medicines Agency
<http://www.ema.europa.eu/pdfs/human/press/pr/24966009en.pdf>

Letter for healthcare professionals sent July 2010
<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON090791>

A2 Calcium gluconate injection in small-volume glass containers: new contraindications due to aluminium exposure risk

Aluminium can be leached from glass after contact with calcium gluconate solution, leading to a risk of exposure to aluminium. Accumulation of aluminium might have adverse effects on bone mineralisation and neurological development in children and those with renal impairment. Calcium gluconate injection packed in small-volume glass containers is now contraindicated for use as repeated or prolonged treatment, including as an intravenous infusion, in children younger than 18 years and in patients with renal impairment. To limit the exposure of patients to aluminium, especially in those with impaired renal function and in children, calcium gluconate injection in small-volume glass containers is also contraindicated in the preparation of total parenteral nutrition solutions. Use of calcium gluconate injection packed in plastic containers is recommended to reduce aluminium burden in vulnerable patients

Authorised use of calcium gluconate injection

Parenteral administration of calcium gluconate is currently authorised where the pharmacological action of a high calcium ion concentration is required—eg, in acute hypocalcaemia, cardiac resuscitation, and in some cases of neonatal tetany.

Calcium gluconate injection in small-volume glass containers: risk of aluminium exposure

Aluminium can be leached from glass after contact with calcium gluconate solution, leading to a risk of exposure to aluminium which might have adverse effects on bone mineralisation and neurological development in children and those with renal impairment. Calcium gluconate injection packed in small-volume glass containers is now contraindicated for use as repeated or prolonged treatment, including as an intravenous infusion, in children younger than 18 years and in patients with renal impairment. To limit the exposure of patients to aluminium, especially in those with impaired renal function and in children, calcium gluconate injection in small-volume glass containers is also contraindicated in the preparation of total parenteral nutrition (TPN) solutions.

The Paediatric Medicines Expert Advisory Group to the Commission on Human Medicines has considered information on the content of aluminium in these preparations. Taking into account evidence that aluminium accumulation might have adverse effects on bone mineralisation and neurological development in children and those with renal impairment, these products should no longer be used for repeated or prolonged treatment of children or those with impaired renal function.

The Group noted that calcium gluconate injection packed in plastic containers is not likely to present a similar risk as the containers do not contain high levels of aluminium.

TPN

The Group was made aware that calcium gluconate injection in small-volume glass containers is also used to provide the calcium element of TPN solutions, although this is not a licensed use. They advised that use of these products for the preparation of TPN should be contraindicated due to the risk of aluminium exposure, especially in vulnerable populations.

Given the use of both licensed and unlicensed products to prepare TPN solutions, we are in discussion with relevant parties within the NHS and other sectors to encourage a transition to the use of calcium gluconate injection packed in containers other than glass.

Advice for healthcare professionals:

- Do not use calcium gluconate injection packed in small-volume glass containers for repeated or prolonged treatment, including as an intravenous infusion, in children younger than 18 years or in patients with renal impairment
- To limit the exposure of patients to aluminium, especially in those with impaired renal function and in children, do not use calcium gluconate injection in small-volume glass containers in the preparation of TPN solutions
- Use of calcium gluconate injection packed in plastic containers is recommended to reduce aluminium burden in vulnerable patients

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Stop press

S1 Modafinil: European Medicines Agency recommends restricted use

Modafinil (Provigil) is a wakefulness-promoting agent.

The European Medicines Agency has recommended that the use of modafinil should be restricted to treat only sleepiness associated with narcolepsy, and that it should no longer be used for the treatment of excessive sleepiness associated with obstructive sleep apnoea or chronic shift work sleep disorder.

On the basis of the available data, the Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of these medicines only outweighed their risks in the therapeutic indication narcolepsy. For all other indications the Committee found that the risks outweighed the benefit shown in clinical trials. Therefore, the Committee concluded that all other indications should be withdrawn from the marketing authorisations of these medicines.

Further information is available from the European Medicines Agency website <http://www.ema.europa.eu/ema/index.jsp>

See also previous advice for modafinil from Drug Safety Update March 2008 <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON014099>

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S2 Rosiglitazone: current advice on cardiovascular risk

We have issued a reminder for healthcare professionals about current advice for the use of **rosiglitazone** (Avandia, Avandamet ▼) in the treatment of diabetes.

In view of the growing evidence of cardiovascular risk with rosiglitazone, healthcare professionals should closely observe the current contraindications, warnings and precautions and monitoring requirements, and consider alternative treatments where appropriate.

c2 Graham DJ, et al. JAMA published online June 28, 2010.
doi:10.1001/jama.2010.920

c3 Nissen SE and Wolski K. Arch Intern Med published online June 28, 2010.
doi:10.1001/archinternmed.2010.207

c4 US Food and Drug Administration. Rosiglitazone cardiovascular safety meta-analyses (see <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugs/AdvisoryCommittee/UCM218495.pdf> July 13–14, 2010)

See European Medicines Agency http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/07/news_detail_001062.jsp

See Central Alerting System <https://www.cas.dh.gov.uk/Home.aspx>

New data c2 c3 c4 have been published that raise concern about an increased risk of cardiovascular adverse effects of rosiglitazone. These data add substantially to existing evidence and point towards an increased cardiovascular risk with rosiglitazone compared with both placebo and with pioglitazone.

A Europe-wide review of available data on the risks and benefits of rosiglitazone by the European Committee on Medicinal Products for Human Use (CHMP) started on July 9, 2010 and is anticipated to be completed by September 2010.

Cardiovascular restrictions

- Rosiglitazone must not be used in patients with current or previous heart failure and in patients with acute coronary syndrome
- The use of rosiglitazone is not recommended in patients with ischaemic heart disease or peripheral arterial disease
- Rosiglitazone and insulin should only be used together in exceptional cases and under close supervision

Monitoring requirements

Patients should be monitored for signs and symptoms of adverse reactions relating to fluid retention, including weight gain and heart failure. Increased monitoring of the patient is recommended if rosiglitazone is used in combination with metformin and insulin.

- Rosiglitazone should be discontinued if any deterioration in cardiac status occurs

Further information for healthcare professionals is available via the Central Alerting System, circulated on July 26, 2010.

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S3 Topical ketoprofen: reminder on risk of photosensitivity reactions

Healthcare professionals are reminded of the risk of photosensitivity reactions associated with **topical ketoprofen**.

The European Medicines Agency Committee for Medicinal Products for Human Use has recently completed a review of the medicine's safety and efficacy, and has concluded that further measures should be put in place to minimise the risk of adverse skin reactions.

Further information can be found on the European Medicines Agency's website.

See European Medicines Agency's website

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2010/07/news_detail_001060.jsp

See Drug Safety Update June 2009 <http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON049070>

Advice for healthcare professionals:

- Patients should ensure that treated areas are protected from sunlight during the whole period of topical ketoprofen treatment and for 2 weeks after stopping treatment; they should also carefully wash their hands after every application
- Patients should stop treatment immediately if they develop any skin reaction after application of these medicines and seek their doctor's advice

- Patients should be informed of the appropriate use of topical ketoprofen as outlined in the product information

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