

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	Piperacillin/tazobactam: compatibility of generics differs from brand leader (Tazocin)	2
	Temsirolimus: severe hypersensitivity reactions during infusion	3
	Tacrolimus (Advagraf and Prograf): risk of serious medication errors	4
Yellow Card Scheme update	You can report side-effects from unlicensed medicines on a Yellow Card	6
Hot topic	Second birthday for European regulation of children's medicines	7
Other information from the MHRA	Patient Information Leaflet of the month: Tanatril	9
	Consultation: reclassification of Flomax to pharmacy (P) availability without prescription	9

The first issue of Drug Safety Update for 2009 highlights the need for care when prescribing and dispensing the immunosuppressant tacrolimus. Confusion between the two different formulations—immediate-release Prograf and prolonged-release Advagraf—has led to medication errors and serious adverse reactions. We would like to remind healthcare professionals of the correct dosing schedules for these formulations (p 4).

Temsirolimus (Torisel) is an analogue of the immunosuppressant sirolimus and is indicated for treatment of renal-cell carcinoma in patients who have at least three of six defined prognostic factors. Hypersensitivity reactions have been associated with administration of this drug. Please read our advice on p 3 regarding: premedication of patients; dilution and administration of this drug; the need for careful monitoring during infusion; and the importance of readily available supportive care.

Finally, you may be interested to read our Hot topic this month (p 7) about European initiatives to improve the availability of medicines for children.

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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Drug safety advice

Piperacillin/tazobactam: compatibility of generics differs from brand leader (Tazocin)

Keywords: piperacillin/tazobactam, compatibility, generics, Tazocin

Generic piperacillin/tazobactam products have different compatibilities with other medicines compared with Tazocin, raising a risk of serious medication errors. Generic piperacillin/tazobactam must **not** be mixed or co-administered with any aminoglycoside, and must **not** be reconstituted or diluted with lactated Ringer's (Hartmann's) solution

For information about the reformulation of Tazocin see Drug Safety Update March 2008, p 3:
www.mhra.gov.uk/mhra/drugsafetyupdate

Piperacillin/tazobactam is licensed for the treatment of a wide range of infections. In addition to the brand leader (called **Tazocin**, which was reformulated in 2008), generic formulations are now available.

Generic piperacillin/tazobactam products have different compatibilities with other medicines compared with Tazocin, raising a risk of serious medication errors.

Advice for healthcare professionals:

- Generic piperacillin/tazobactam must **not** be mixed or co-administered with any aminoglycoside, and must **not** be reconstituted or diluted with lactated Ringer's (Hartmann's) solution
- Pharmacists should clearly label reconstituted generic piperacillin/tazobactam with a statement that the product must not be mixed or co-administered with aminoglycosides
- Prescription charts should be checked to ensure that where patients are prescribed both aminoglycosides and generic piperacillin/tazobactam these are not administered at the same time because this can lead to inactivation of the aminoglycoside. Clinical and nursing staff should be advised of the risks with these products
- Generic piperacillin/tazobactam is **not** compatible with lactated Ringer's (Hartmann's) solution
- If you are in doubt about which piperacillin/tazobactam medicine is in use, contact a hospital pharmacist before reconstitution or administration

Marketing authorisation holders for generic piperacillin/tazobactam are providing educational materials for healthcare professionals, including: guidance for pharmacists; posters for display in pharmacy-run CIVAS (Centralised Intravenous Additive Service) units; posters for display in nursing and clinical areas; and a training pack for all professionals who have a role in the supply and administration of these medicines.

Please remember that you can report suspected adverse events to medicines using a Yellow Card at www.yellowcard.gov.uk

Temsirolimus: severe hypersensitivity reactions during infusion

Keywords: temsirolimus, Torisel, hypersensitivity reactions, infusion-related reactions, advanced renal-cell carcinoma

Severe infusion-related hypersensitivity reactions have occurred in patients receiving temsirolimus. Patients must be closely monitored throughout infusion, and appropriate supportive care should be available

See section 5.1 of the Summary of Product Characteristics for prognostic factors; <http://emc.medicines.org.uk/>

¹ Hudes G, et al. *N Engl J Med* 2007; **356**: 2271–81.

Temsirolimus (Torisel▼) is an antineoplastic agent used to treat patients with advanced renal-cell carcinoma who have at least three of six prognostic risk factors.

Infusion-related hypersensitivity reactions have occurred during the administration of temsirolimus. The reactions include, but are not limited to, flushing, chest pain, dyspnoea, hypotension, apnoea, loss of consciousness, and anaphylaxis. Up to April 3, 2008, the marketing authorisation holder for Torisel had received 46 spontaneous reports of infusion-related hypersensitivity reactions, one of which had a fatal outcome.

In a pivotal clinical trial¹ in renal-cell cancer, 18 (9%) of 208 of patients treated with temsirolimus experienced allergic reactions of any severity. In all clinical trials to date, about 1% of patients treated with temsirolimus have experienced serious hypersensitivity or infusion reactions.

Most reactions have occurred with the first infusion, commonly within the first few minutes of the start of the infusion; however, reactions with subsequent infusions have also been reported. In some cases, the reactions occurred despite patients having received antihistamine premedication.

Advice for healthcare professionals:

- Refer to the Summary of Product Characteristics instructions for pre-medication of patients, and for dilution and administration of temsirolimus
- Patients should receive 25–50 mg diphenhydramine intravenously (or similar antihistamine) approximately 30 min before the start of every dose of temsirolimus
- Patients must be closely monitored throughout infusion, and appropriate supportive care should be available
- Temsirolimus infusion should be interrupted in all patients who have severe infusion reactions and appropriate medical care given. The patient should be observed for at least 60 min
- Temsirolimus therapy should only be resumed in patients who experience severe or life-threatening reactions after a careful consideration of risks and benefits for the individual
- If infusion is to be resumed, diphenhydramine (or similar antihistamine) and an H₂-receptor antagonist (20 mg famotidine intravenously or 50 mg ranitidine intravenously) should be administered approximately 30 min before restarting temsirolimus infusion. Administration of corticosteroids may be considered; however, the efficacy of corticosteroid treatment in this setting has not been established. Infusion may then be resumed at a slower rate (up to 60 min) and should be completed within 6 h from the time that temsirolimus is first added to sodium chloride 9 mg/mL (0.9%) solution for injection

Tacrolimus (Advagraf and Prograf): risk of serious medication errors

Keywords: tacrolimus, Advagraf, Prograf, transplant, graft rejection

Prograf and Advagraf are not interchangeable and should not be substituted without careful therapeutic monitoring

Prograf and Advagraf contain the immunosuppressant tacrolimus, which has a narrow therapeutic index.

Prograf:

- is indicated for prophylaxis of transplant rejection in allograft recipients of a liver, kidney, or heart, and for treatment of allograft rejection that is resistant to treatment with other immunosuppressants
- is an **immediate-release** formulation intended for twice-daily dosing, once in the morning and once in the evening

Advagraf:

- is indicated for prophylaxis of transplant rejection in allograft **adult** recipients of a liver or kidney, and for treatment of allograft rejection in **adults** who are resistant to treatment with other immunosuppressants
- is a **prolonged-release** formulation for once-daily administration in the morning

Prograf was licensed in 1994 and is available as 0.5 mg, 1 mg, and 5 mg capsules. It should be given twice a day (once in the morning and once in the evening; dose is based on patient weight). In 2007, a modified-release formulation of tacrolimus became available under the brand name Advagraf. This formulation is also available in 0.5 mg, 1 mg, and 5 mg capsules, but should be taken once a day in the morning (dose is based on patient weight).

Reports of serious medication error

As of Dec 10, 2008, medication errors with Advagraf and Prograf have been reported in seven EU countries; most reports were from the UK. Errors have fallen into one of three categories:

- Prescribing errors by hospital doctor or GP (six reports)
- Dispensing errors by pharmacist related to generic or brand prescribing (41 reports)
- Administration errors by doctor, nurse, or patient (eight reports)

These errors have in some cases resulted in patients being dosed incorrectly, and have led to serious adverse reactions—including biopsy-confirmed acute rejection of transplanted organs—or other side-effects which could be a consequence of either under exposure or over exposure to tacrolimus. Four serious cases have been reported to the manufacturer.

Prograf and Advagraf are not interchangeable without careful therapeutic monitoring. Substitution should be made only under the close supervision of a transplant specialist. Particular care should be taken in prescribing and dispensing

the correct brand of tacrolimus (ie, Prograf or Advagraf). Prescribers, pharmacists, and patients should be fully aware of the brand being prescribed and the associated correct dose regimen.

Temporary changes are being made to the outer packaging of Advagraf to highlight the once-daily dose regimen, and the updated packs should be available on stock supplied from January 2009. Further changes to the labelling are planned to come into effect by April 2009.

Advice for healthcare professionals:

- **Prograf** is an immediate-release formulation that must be taken twice a day: once in the morning and once in the evening
- **Advagraf** is a modified-release formulation that must be taken once a day in the morning
- The indications for Advagraf and Prograf are not identical (see box above). Advagraf is licensed for use in adults only
- Care should be taken to ensure the correct brand of tacrolimus is prescribed and dispensed
- Prograf and Advagraf should not be interchanged without careful therapeutic monitoring, and should be done only under the close supervision of a transplant specialist

See also a letter sent to healthcare professionals in December 2008:
<http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/index.htm>

Yellow Card Scheme update

For information about melanotan, see Drug Safety Update December 2008 p 8: www.mhra.gov.uk/mhra/drugsafetyupdate

For more information on black cohosh visit the MHRA website at <http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/HerbalSafetyNews/Currentsafetyissues/CON2024131>

To tell us about the sale of unlicensed medicines call our Information Centre in confidence on 020 7084 2000.

For more information on borderline products see <http://www.mhra.gov.uk/Howweregulate/Medicines/Doesmyproductneedalicense/Borderlineproducts/index.htm>; download a 'borderline advice form' from this webpage.

For more information about herbal products see <http://www.mhra.gov.uk/Howweregulate/Medicines/Herbalandhomoeopathicmedicines/Herbalmedicines/index.htm>

You can report side-effects from unlicensed medicines on a Yellow Card

In last month's Drug Safety Update, we highlighted the potential risks from the use of melanotan—a medicine in the UK that is not licensed, but is being used by consumers in the hope of achieving a fake 'suntan'.

The risks and potential side-effects from using unlicensed products such as melanotan are not known. Reporting on a Yellow Card any potential side-effects from using an unlicensed medicine is one way that we can find out more information about these products and take action to safeguard public health.

If you are aware of a patient who may have had an adverse reaction from an unlicensed medicine, please complete a Yellow Card on their behalf or encourage them to complete one. Healthcare professionals and consumers can report online at www.yellowcard.gov.uk. If available, please include the unlicensed product name, active ingredients, and where it was obtained. All Yellow Card reports we receive are treated in strict confidence and will only be used to help safeguard public health.

It is also important to note that it is illegal to sell or advertise an unlicensed medicine such as melanotan in the UK. You can tell the MHRA in confidence if you wish to report potentially illegal supply and promotion.

Most medicines are clearly identifiable, but there are some products which can be difficult to distinguish from a cosmetic or food. Dietary supplements that contain vitamins, aminoacids, or minerals are usually subject to food safety and labelling legislation, but a product that contains a pharmacologically active substance or that makes medicinal claims might be subject to medicines control. The MHRA can offer advice on the status of a product under medicines legislation if in doubt.

Some herbal remedies on the market may be unlicensed. However, it is important to note that it is legal to sell and supply unlicensed herbal remedies as long as no medicinal claims are made on the packaging. We accept Yellow Cards that report suspected side-effects from any herbal remedy, whether licensed or unlicensed. In July 2006, information from the Yellow Card Scheme provided supporting evidence for a risk of serious adverse liver reactions with the use of products that contained black cohosh (*Cimifuga racemosa*). This resulted in label warnings on both licensed and unlicensed products containing black cohosh.

Remember that by reporting suspected adverse drug reactions through the Yellow Card Scheme you can help safeguard public health.

Hot topic

Second birthday for European regulation of children's medicines

It has been recognised for a considerable time that children have been disadvantaged when it comes to treatment with medicines. Many medicines given to children have not been properly studied in this age-group, and are used 'off-label' — outside their authorised indications — or are completely unlicensed.

What special challenges do children's medicines pose?

Although there may be ethical concerns about conducting trials in children, there are equal concerns about giving medicines to a population in which they have not been tested. Specific trials in children are needed because of age-related differences in drug handling or drug effects, or indeed the nature of the disease itself, which may lead to different dose requirements to achieve efficacy and avoid adverse effects.

An additional challenge for children's medicines is the need to develop suitable age-appropriate formulations that provide the correct dose and that are palatable to the patient. Incentives are needed to encourage industry to develop what may be technically difficult products.

What initiatives have been taken?

New legislation...

Both Europe and the USA have introduced legislation to improve the availability of high-quality, ethically researched and properly authorised medicines for children.

This January is the 2nd anniversary of the European Paediatric Regulation coming into force. Its key provisions include:

- a new European scientific committee dedicated to paediatric medicines
- obligations on companies developing new medicines to design studies in children, where appropriate (known as Paediatric Investigation Plans, PIPs)
- rewards (through extension of patent-protection periods) for conducting these studies
- rewards (through market exclusivity) for new paediatric uses for off-patent medicines
- assessment of existing data on the use of medicines in children not previously submitted to regulatory authorities

...and progress

The European Paediatric Committee has been set up, and includes representation from regulatory authorities, healthcare professionals, and patients. To date, the Committee has considered nearly 600 PIPs of which 63% have been for brand new medicines and 34% are for existing patented products. 3% are for new uses of off-patent products. These plans cover a wide range of therapeutic areas and the first marketing authorisation applications supported by studies in PIPs have been received.

EU Paediatric Regulation
http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf

Access a Public Assessment Report for the licensing of caffeine citrate at <http://www.mhra.gov.uk/home/groups/-unit1/documents/websiteresources/con014685.pdf>; for important safety information on caffeine citrate see Drug Safety Update August 2008, p 9. Access a Public Assessment Report for fentanyl at <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/index.htm> (scroll down to heading "Assessment reports of paediatric data – EU worksharing exercise"); for safety information on fentanyl patches see Drug Safety Update September 2008, p 2; www.mhra.gov.uk/mhra/drugsafetyupdate

The EU Directive on clinical trials outlines requirements that protect children who participate in trials: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_20/dir_2001_20_en.pdf

For more information on updates to product information for use in children see <http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/index.htm>

And in the UK?

A number of new medicines for children have been introduced in the UK. Examples include caffeine 5 mg/mL solution for injection (as citrate) for treatment of apnoea of prematurity, and the addition of dose instructions for children to the product information for fentanyl patches in the treatment of opioid-tolerant patients with chronic intractable pain.

Encouraging coordinated clinical research

The new Regulation further encourages high-quality clinical research in children, and sharing of experience across Europe, to avoid unnecessary duplication of studies. Specifically:

- information on clinical trials in children will be made public later in 2009
- information will be made available on the outcome of studies in children, irrespective of whether the medicine has shown to be effective
- priority lists for research areas have been developed and research funding provided for off-patent medicines

Furthermore, plans for coordinating European paediatric research networks are in place. A highly successful Medicines for Children Research Network, with now over 100 studies in its portfolio, has been established in the UK and will participate in the European network.

Better information

The British National Formulary for Children was introduced in 2005 with information on both licensed and unlicensed treatments.

We continue to update Summaries of Product Characteristics and Patient Information Leaflets with information on use of a particular medicine in children, with the aim of achieving consistent information for different products that have the same active ingredient.

Further information

MHRA information on medicines for children:

<http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesforchildren/index.htm>

European Medicines Agency information on medicines for children:

<http://www.emea.europa.eu/htms/human/paediatrics/introduction.htm>

European Commission:

http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/medchild_en.htm

US Food and Drug Administration information on paediatric drug development:

<http://www.fda.gov/Cder/pediatric/index.htm>

UK Children's National Service Framework:

http://www.dh.gov.uk/en/Healthcare/NationalServiceFrameworks/Children/DH_4089111

UK Medicines for Children Research Network: <http://www.mcrn.org.uk/>

British National Formulary for Children: <http://bnfc.org/bnfc/>

Royal College of Paediatrics and Child Health: <http://www.rcpch.ac.uk/>

Other information from the MHRA

Patient Information Leaflet of the month: Tanatril

[http://www.mhra.gov.uk/Howweregulate/Medicines/Labelpatientinformationleafletsandpackaging/Patientinformationleaflet\(PIL\)ofthemonth/index.htm](http://www.mhra.gov.uk/Howweregulate/Medicines/Labelpatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm)

Patient information leaflets (PILs) are improving in quality as a result of new legal obligations on manufacturers to test the documents with potential patients. Testing makes sure that the presentation of the information enables patients to find and understand key messages for safe use about the medicine within the PIL and thereby enable them to use the medicine safely and effectively. To promote this new initiative, we are publishing a series of examples of best practice on our website. The latest in the series is for **Tanatril** (imidapril), an ACE inhibitor indicated for the treatment of high blood pressure.

Consultation: reclassification of Flomax to pharmacy (P) availability without prescription

To read more about the consultation visit <http://www.mhra.gov.uk/Publications/Consultations/Medicinesconsultations/ARMs/CON031154>;

to respond with your views by Jan 15, 2009, email reclassification@mhra.gsi.gov.uk

We wish to seek your views on the reclassification from prescription-only medicine (POM) to pharmacy (P) availability of Flomax (**tamsulosin**) for treatment of benign prostatic hyperplasia in men age 45 years or older. Pharmacy availability would involve supply of once-daily 0.4 mg tamsulosin for 2–10 weeks in accordance with a protocol based on a patient questionnaire; after 10 weeks, tamsulosin will be supplied only if a doctor has confirmed a diagnosis of benign prostatic hyperplasia.

Comments on this proposed reclassification should be sent by Jan 15, 2009.

Read more about the Commission on Human Medicines, including summaries of minutes from meetings, at www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines

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