# 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

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**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.

Professionals who prescribe antidepressants will wish to be aware of our information this month regarding data from epidemiological studies which suggest an increased risk of persistent pulmonary hypertension in the newborn of mothers receiving SSRIs in pregnancy (particularly later stages, p 2). Although there is no evidence for an association between SNRIs and PPHN, a potential risk cannot be ruled out given the related mechanism of action. We also have information on epidemiological data suggesting an increased risk of bone fractures in patients receiving SSRIs or TCAs (p 3).

Also this month, a review of data for carbapenems, a class of beta-lactam antibiotics, has shown a clinically significant interaction with valproic acid/sodium valproate, which results in significantly reduced valproate plasma concentrations with potential for inadequate seizure control. Concomitant use of carbapenems and valproic acid/sodium valproate is not recommended, and prescribers should consider alternative antibacterial therapy (p 4).

On p 6, we inform you that the simvastatin product information now recommends that the 80-mg dose should be considered only in 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 the potential risks.

The risk of medication errors with oral tacrolimus remains a source of concern, which is compounded by the introduction of the first generic oral immediate-release tacrolimus product. There are currently three different formulations of tacrolimus: they are not interchangeable and it is not safe to switch between these formulations without careful therapeutic monitoring and supervision. Read our advice on p 5 to support safer use of oral tacrolimus.

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# SSRIs and SNRIs: risk of persistent pulmonary hypertension in the newborn

**Keywords:** SSRIs, selective serotonin reuptake inhibitors, SNRIs, serotonin and noradrenaline reuptake inhibitors, persistent pulmonary hypertension in the newborn, PPHN

**Epidemiological data suggest that the use of SSRIs in pregnancy, particularly in the later stages, may increase the risk of persistent pulmonary hypertension in the newborn. Healthcare professionals are encouraged to enquire about the use of SSRIs and SNRIs, particularly in women in the later stages of pregnancy. Close observation of neonates exposed to SSRIs or SNRIs for signs of PPHN is recommended after birth**

For further information see monthly report from the EU Pharmacovigilance Working Party at http://www.ema.europa.eu/pdfs/human/phvwp/17301110en.pdf

Selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are antidepressant medicines. A review of epidemiological data has suggested that the use of SSRIs in pregnancy, particularly in the later stages, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately five cases per 1000 pregnancies whereas the background rate in the general population is one to two cases of PPHN per 1000 pregnancies. PPHN presents as severe hypoxaemia due to pulmonary artery hypertension.

1 Chambers CD, et al. *New Engl J Med* 2006; **354:** 579–87.

A retrospective study by Chambers and colleagues[1] reported an increased risk of PPHN in those exposed after 20 weeks' gestation (odds ratio 6·1 [95% CI 2·2–16·8]), but no increased risk of PPHN in fetuses exposed to SSRIs before 20 weeks' gestation.

2 Kallen B, Olausson PO. *Pharmacoepidemiol Drug Saf* 2008; **17:** 801–06.

A recent epidemiological study conducted by Kallen and Olausson[2] aimed to verify the observation of an association between maternal use of SSRIs and PPHN using exposure information recorded before the pregnancy outcome was known. The study was based on the Swedish medical birth register covering 1997–2005: infants born to women who had used an SSRI during pregnancy during this period were compared with all other infants recorded in the birth register for those years (n=831 324).

After adjustment, an association between maternal SSRI use and PPHN in births after 34 weeks of gestation carried a risk ratio of 2·4 (95% CI 1·2–4·3) based on women who reported SSRI use in early pregnancy. From a subgroup who also had prescriptions for an SSRI from antenatal care later in pregnancy, the risk estimate was 3·6 (1·2–8·3).[2]

Although there is no evidence for the association of PPHN to SNRI treatment, this potential risk cannot be ruled out taking into account the related mechanisms of action.

**Advice for healthcare professionals:**

- Healthcare professionals, including midwives, should be aware of the increased risk of PPHN associated with all SSRIs and potentially with SNRIs. The observed increase in risk is about an extra 3–4 cases of PPHN per 1000 pregnancies
- In light of these new data, healthcare professionals are encouraged to enquire about the use of these medicines, particularly in women in the later stages of pregnancy
- Close observation of neonates exposed to SSRIs or SNRIs for signs of PPHN is recommended after birth

# Antidepressants: risk of fractures

**Keywords:** antidepressant, fractures, SSRIs, selective serotonin reuptake inhibitors, TCAs, tricyclic antidepressants

**Healthcare professionals should be aware of epidemiological data showing a small increased risk of fractures associated with the use of TCAs and SSRIs, and should take this risk into account in their discussions with patients and in prescribing decisions**

For further information see monthly report from the EU Pharmacovigilance Working Party at http://www.ema.europa.eu/pdfs/human/phvwp/17301110en.pdf

1 Liu B, et al. *Lancet* 1998; **351:** 1303–07.
2 Hubbard R, et al. *Am J Epidemiol* 2003; **158:** 77–84.
3 French DD, et al. *Drugs Aging* 2005; **22:** 877–85.
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5 Bolton JM, et al. *J Clin Psychopharmacol* 2008; **28**: 384–90.
6 Ensrud KE, et al. *Arch Intern Med* 2003; **163:** 949–57.
7 Richards JB, et al. *Arch Intern Med* 2007; **167:** 188–94.
8 Ziere G, et al. *J Clin Psychopharmacol* 2008; **28**: 411–17.
9 van den Brand MW, et al. *Osteoporos Int* 2009; **20:** 1705–13.
10 Haney EM, et al. *Bone* 2009. Published online Aug 5, 2009. doi.org/10.1016/j.bone.2009.07.083.
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14 Hartikainen S, et al. *J Gerontol Med Sci* 2007; **62A:** 1172–81.
15 Thapa PB, et al. *N Engl J Med 1998*; **339:** 875–82.
16 Landi F, et al. *J Gerontol A Biol Sci Med Sci* 2005; **60:** 622–26.
17 Williams LJ, et al. *Int Clin Pscyhopharmacol* 2008; **23:** 84–87.
18 Mezuk B, et al. *J Gerontol A Biol Sci Med Sci* 2008; **63:** 1410–15.
19 Haney EM, et al. *Arch Intern Med* 2007; **167:** 1246–51.
20 Diem SJ, et al. *Arch Intern Med* 2007; **167:** 1240–45.
21 Kinjo M, et al. *Am J Med 2005*; **118:** 1414.e7–e12.
22 Spangler L, et al. *J Gen Intern Med* 2008; **23:** 567–74.

A review of epidemiological studies, mainly in patients age 50 years or older, shows an increased risk of bone fractures in patients receiving SSRIs (selective serotonin reuptake inhibitors) and TCAs (tricyclic antidepressants). The mechanism leading to this increased risk is unclear.

Nine reviewed observational studies[1–9] give a range of odds ratios for fractures associated with current use of SSRIs (irrespective of dose or duration of use) between 1·4 (95% CI 0·93–2·24) and 2·4 (2·0–2·7). These risks were significant in most studies. The odds ratios for studies that included TCAs varied between 1·2 (0·7–2·2) and 2·2 (1·8–2·8), and in all but one study were lower than the estimates for SSRIs.

Six of the nine studies assessed dose response and observed a trend more consistently for SSRIs compared with TCAs. Six of the nine studies assessed duration of use and found that the risk of fracture associated with SSRIs seems to increase initially to a peak within the first 6–12 months; risk subsequently decreases, but remains elevated with prolonged use (>1·5 years). Risk with TCAs peaks shortly after initiation (1–2 months) and disappears after prolonged use (>6–12 months). The persistence of the effect after cessation of use was assessed in four of the nine studies. The increased risk observed for SSRIs and TCAs disappears relatively shortly after discontinuation (3–12 months). None of the studies investigated the effects of dose and duration simultaneously.

## Risk of falls

The relationship between SSRIs and fall risk is not clear.[10] Several studies show that SSRI use is associated with an increased fall risk, and that this risk is higher than for other types of antidepressants, including mainly TCAs.[3,7,11–14] However, other studies show that SSRIs confer equivalent or lower fall risk to TCAs.[6,15] An Italian study of patients receiving home care showed no increased risk of falls with any antidepressant.[16]

## SSRIs and decreased bone mineral density

Some studies[17–20] have found an association between antidepressant use and decreased bone mineral density; however, other studies have found no such association.[21,22]

## Conclusions of the review

Taking into account the strengths and limitations of the available evidence, the review concluded that product information should be updated with a statement on epidemiological findings of an increased risk of bone fractures with TCAs and SSRIs.

From the available data, no definite conclusions could be drawn regarding a dose-response relation, time relation, or the underlying mechanism.

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**Advice for healthcare professionals:**

- A review of epidemiological studies, mainly in patients age 50 years or older, shows an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this increased risk is unclear
- Healthcare professionals should be aware of a small increased risk of fractures associated with the use of TCAs and SSRIs, and should take this risk into account in their discussions with patients and in prescribing decisions

## Carbapenems: concomitant use with valproic acid not recommended

**Keywords:** valproic acid, sodium valproate, carbapenems, doripenem, ertapenem, imipenem-cilastatin, meropenem, antibacterials, anticonvulsant, seizure

**A clinically significant interaction between carbapenems and valproic acid results in reduced valproate plasma concentrations with potential for inadequate seizure control. Concomitant use of these agents is not recommended, and healthcare professionals should consider alternative antibacterial therapy**

Carbapenems are a class of beta-lactam antibiotics with broad-spectrum antibacterial activity. They are indicated for the treatment of the following infections when caused by susceptible bacteria: nosocomial pneumonia; complicated intra-abdominal infections; and complicated urinary tract infections. Valproic acid/sodium valproate is an anticonvulsant used for the treatment of generalised, partial, or other epilepsy.

Four carbapenems are authorised in the UK: doripenem (Doribax▼); ertapenem (Invanz▼); imipenem-cilastatin (Primaxin); and meropenem (Meronem). Summaries of Product Characteristics are available at http://emc.medicines.org.uk/.

An interaction between carbapenems and valproic acid has been described in a number of case reports and one identified study.[1] The mechanism of the interaction has not been elucidated; however, several potential mechanisms have been proposed in the literature.[2]

A more-recent unpublished pharmacokinetic study of 24 healthy human volunteers found that concomitant administration of valproic acid and doripenem resulted in a rapid and substantial fall in plasma valproate levels. Given the large magnitude and rapid time course of this interaction, monitoring of sodium valproate levels or making dose adjustments are unlikely to manage this interaction, which could lead to inadequate seizure control.

A Europe-wide class review of data for the remaining carbapenems found that decreased valproic acid levels have also been reported when co-administered with other carbapenems, with 60–100% decreases in valproic acid levels being observed within about 2 days. This interaction is therefore likely to be a class effect.

Concomitant use of carbapenems and valproic acid/sodium valproate is not recommended, and prescribers should consider alternative antibacterial therapy.

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1 Spriet I, et al. *Ann Pharmacother* 2007; **41:** 1130–36.

2 Mori H, et al. *Drug Metab Rev* 2007; **39:** 647–57.

For further information see monthly report from the EU Pharmacovigilance Working Party at http://www.ema.europa.eu/pdfs/human/phvwp/3313810en.pdf

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**Advice for healthcare professionals:**

- A clinically significant interaction between carbapenems and valproic acid/sodium valproate results in reduced valproate plasma concentrations with potential for inadequate seizure control
- Given the large magnitude and rapid time course of this interaction, monitoring of sodium valproate levels or making dose adjustments are unlikely to manage this interaction
- Concomitant use of carbapenems in patients taking valproic acid/sodium valproate is not recommended, and prescribers should consider alternative antibacterial therapy

## Oral tacrolimus products: measures to reduce risk of medication errors

**Keywords:** tacrolimus, Modigraf, Prograf, Advagraf, Adoport

**There are three different formulations of tacrolimus; they are not interchangeable. To minimise medication errors arising from different formulations of tacrolimus, prescribers should either: provide full information, stating on the prescription the drug, the exact pharmaceutical form (capsules or granules; immediate-release or prolonged-release), the strength, and the posology (dose and dose frequency); or prescribe by brand name and include the strength and posology (dose and dose frequency). Patients should take note of the name of their tacrolimus medicine and the dose that has been prescribed for them**

### Medication errors

Tacrolimus is an immunosuppressant with a narrow therapeutic index, which may be given orally to prevent or treat organ transplant rejection.

Since 2008, the MHRA has become aware of medication errors due to the unintended switching of different formulations of the original branded oral tacrolimus products in patients who have been treated with tacrolimus for the prevention of organ transplant rejection. Graft rejection reactions and tacrolimus toxicity have resulted from a small number of these medication errors.

By the end of February 2010, the MHRA had received 12 case reports involving prescribing/dispensing errors in association with oral tacrolimus. These included: four cases of acute rejection reaction; three cases of increased drug levels; and two cases of increased creatinine.

See Drug Safety Update January 2009, p 4; www.mhra.gov.uk/drugsafetyupdate

In January 2009 we published advice in Drug Safety Update on the need for close supervision and monitoring of any change to the prescribed tacrolimus product or dose regimen. We also advised that great care was needed when prescribing and dispensing oral tacrolimus to ensure that the patient receives the intended formulation and the correct dose. The risk of medication errors remains a source of concern, which is compounded by the launch of a novel formulation containing tacrolimus (Modigraf granules for oral suspension) and the introduction, taking place currently, of the first generic oral immediate-release tacrolimus product (Adoport capsules). Other generics are likely to follow.

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**Important: There are three different formulations of tacrolimus; it is not safe to switch between these formulations:**

- Prograf and Adoport are **immediate release capsule** formulations taken **twice daily**. Generic immediate-release tacrolimus capsules are bioequivalent with Prograf and may be interchanged
- Advagraf is a **prolonged release capsule** formulation taken **once daily**
- Modigraf is a **granule** formulation taken **twice daily** but is **not** bioequivalent with Prograf or Advagraf

These three formulations are not interchangeable; switching between the different formulations of oral tacrolimus requires careful therapeutic monitoring, and the close supervision of a transplant specialist. Unsupervised switching can lead to underdosing or overdosing of tacrolimus, and risks transplant rejection or adverse reactions.

### Prescribing oral tacrolimus products

In order to minimise the risk of future medication errors and unintended switching between the different formulations, the Commission on Human Medicines and the MHRA recommend that prescribers should either: provide full information, stating on the prescription the drug, the exact pharmaceutical form (capsules or granules; immediate-release or prolonged-release), the strength, and the posology (dose and dose frequency); or prescribe by brand name and include the strength and posology (dose and dose frequency). To aid prescribers all generic oral tacrolimus products will be approved with a brand name.

*Example of prescribing information for oral tacrolimus*

Prescribing information for an oral tacrolimus medicine should be written as follows:

*"Tacrolimus 1 mg prolonged-release capsules. One to be taken once daily"*

Or

*"Advagraf 1 mg. One to be taken once daily"*

If the exact pharmaceutical form and strength or brand and strength of tacrolimus is not clearly stated on the prescription, the dispensing pharmacist should check with the prescriber to ensure that the appropriate medicine is dispensed.

Patients should be advised to take careful note of the name of the tacrolimus medicine and the dose that they are taking, and should check with their doctor or pharmacist if they receive an unfamiliar medicine or if they have questions about the dose.

### Changing oral tacrolimus products

This recommendation must not be taken to imply that a patient's treatment may not be changed to an alternative tacrolimus product or formulation. However, changes between different formulations, and changes in dosing regimen, should always be accompanied by careful therapeutic monitoring under the supervision of a transplant specialist.

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**Advice for healthcare professionals:**

- To minimise medication errors arising from different formulations of tacrolimus, prescribers should either: provide full information, stating on the prescription the drug, the exact pharmaceutical form (capsules or granules; immediate-release or prolonged-release), the strength, and the posology (dose and dose frequency); or prescribe by brand name and include the strength and the posology (dose and dose frequency)
- Pharmacists should always dispense the exact pharmaceutical form and strength or brand and strength of oral tacrolimus that has been prescribed, and should contact the prescriber if the prescriber's intention is not clear, to ensure that the appropriate medicine is dispensed
- Switching between tacrolimus formulations requires careful medical supervision, and therapeutic monitoring
- Patients should be advised to take careful note of the name of their tacrolimus medicine and the dose that they are taking, and should check with their doctor or pharmacist if they receive an unfamiliar medicine or if they have questions about the dose

## Simvastatin: increased risk of myopathy at high dose (80 mg)

**Keywords:** simvastatin, Zocor, Inegy, myopathy, statins, lipids, cardiovascular disease

**There is an increased risk of myopathy associated with high-dose (80 mg) simvastatin. The 80-mg dose should be considered only in 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 the potential risks**

The simvastatin (Zocor) product information (Summary of Product Characteristics and Patient Information Leaflet) has been updated to include warnings about increased risk of myopathy in patients receiving the highest licensed dose (80 mg). Similar changes are being implemented to the product information for combination products that contain simvastatin, such as Inegy (simvastatin combined with ezetimibe).

### SEARCH data

For interim details of SEARCH, see: SEARCH Study Collaborative Group. *Am Heart J* 2007; **154:** 815–23.e6.

This update follows a review of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH). SEARCH was a multicentre, double-blind, active-treatment, factorial-design study conducted at 88 sites in the UK, which evaluated the effect of treatment with Zocor 80 mg versus 20 mg on major vascular events (MVEs, defined as fatal coronary events, non-fatal myocardial infarction, coronary revascularisation procedure, non-fatal or fatal stroke, or peripheral revascularisation procedure) in 12 064 patients with a history of myocardial infarction, over a median follow-up of 6·7 years.

The results showed that treatment with simvastatin 80 mg did not provide any significant benefits over simvastatin 20 mg. The incidence of MVEs was similar for 80 mg (1477, 24·5%) versus 20 mg (1553, 25·7%; risk ratio 0·94 [95% CI 0·88–1·01]). There was no evidence of increased total or cause-specific

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For some suspected rhabdomyolysis cases there were no detailed data to confirm 100% diagnosis according to the criteria used.

mortality, vascular mortality, non-vascular mortality, or higher risk of cancer or haemorrhagic stroke with the high dose of simvastatin. However, myopathy occurred in 52 patients (0·9%) randomly assigned simvastatin 80 mg compared with one patient (0·02%) randomly assigned simvastatin 20 mg. An estimated 11 patients in the simvastatin 80-mg group developed rhabdomyolysis compared with none in the simvastatin 20-mg group.

### Myopathy

Myopathy is a known side effect of all statins, including simvastatin, and the risk increases with higher doses. However, its most serious form, rhabdomyolysis is a very rare side effect. The risk of myopathy is greater in: elderly patients (>65 years); women; patients with renal impairment or hypothyroidism; patients who consume large quantities of alcohol; those with a history of previous muscle problems during treatment with statins or other lipid-lowering drugs; or those with family history of muscle disorders. Concomitant use of some medicines may also increase the risk of muscle damage.

**Advice for healthcare professionals:**

- Simvastatin 80 mg should be considered only in 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 the potential risks
- Prescribers treating patients who are taking simvastatin 80 mg or who are being considered for an up-titration to that dose may need to review their treatment during their next visit, to take into account the new evidence
- Patients who are currently taking simvastatin 80 mg should not stop taking their medicine. However, they should be advised to contact their doctor immediately if they experience unexplained muscle pain, tenderness, or weakness
- Please report suspected adverse reactions with medicines, including statins, to us via the Yellow Card Scheme (www.yellowcard.gov.uk)

# Stop press

## Panitumumab (Vectibix): serious hypersensitivity reactions

**Panitumumab** (Vectibix) is indicated as monotherapy for the treatment of patients with EGFR (epidermal growth factor receptor)-expressing metastatic colorectal carcinoma with non-mutated (wild type) *KRAS* after failure of chemotherapy regimens.

There have been new reports of serious hypersensitivity reactions (including anaphylaxis) in patients receiving panitumumab, some of which were fatal. A clinical trial report has been received of a fatal case of angioedema occurring 2 days after exposure following a prior episode of angioedema which occurred 6 days after exposure. Recently, two case reports of fatal hypersensitivity reactions during and immediately following panitumumab infusion have been received; these patients had previously experienced hypersensitivity reactions to cetuximab and oxaliplatin, respectively.

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Product information has been updated to highlight the following:

**Advice for healthcare professionals:**

- Panitumumab is contraindicated in patients with a history of severe or life-threatening hypersensitivity reactions to this medicine
- Serious infusion-related reactions are unpredictable and can occur suddenly. Panitumumab should be permanently discontinued if a severe or life-threatening reaction occurs
- In patients with a mild or moderate infusion-related reaction, the infusion rate should be reduced for the duration of the infusion; it is recommended to maintain this lower infusion rate in all subsequent infusions
- Hypersensitivity reactions occurring more than 24 hours after infusion have also been reported. Patients should be warned of a possible late-onset reaction and instructed to contact their physician if symptoms of hypersensitivity occur

See http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON081746

A letter has been sent to relevant healthcare professionals to inform of these risks.

# Other information from the MHRA

## PIL of the month: Durogesic D Trans Transdermal Patch

Access PIL of the month at http://www.mhra.gov.uk/Howweregulate/Medicines/Labelspatientinformationleafletsandpackaging/Patientinformationleaflet(PIL)ofthemonth/index.htm

For further information to support safer use of fentanyl patches, see Drug Safety Update September 2008, p 2; www.mhra.gov.uk/drugsafetyupdate

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 supporting safer use of the medicine within the PIL and thereby enables 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 example in the series is the leaflet for **Durogesic D Trans Transdermal Patch**, which contains **fentanyl**—a potent opioid analgesic used in the management of chronic intractable pain. The leaflet has recently been redesigned to clarify the posology for these patches and uses good navigation tools. In testing the leaflet was well received by patients.

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