

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**

Volume 6, Issue 3, October 2012

Contents

Drug safety advice	Agomelatine (Valdoxan/Thymanax): risk of dose-related hepatotoxicity and liver failure – updated warnings and monitoring guidance	A1
	Intravenous 0.18% saline/4% glucose solution ('hypotonic saline') in children: reports of fatal hyponatraemia – do not use in children aged 16 years or less, except in specialist settings under expert medical supervision	A2
	Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment – monitoring recommended	A3
Hot topics	Simvastatin: evidence supporting recent advice on dose limitations with concomitant amlodipine or diltiazem	H1
	Pseudoephedrine and ephedrine: update on managing risk of misuse	H2
Stop press	Non-steroidal anti-inflammatory drugs (NSAIDs): further evidence that the cardiovascular risk with diclofenac is higher than other non-selective NSAIDs and similar to the selective COX-2 inhibitors	S1
Other information from the MHRA	Learning about reducing medicines risk - Antipsychotics	O1

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.



For full details on our accreditation visit **NHS Evidence**

<http://www.evidence.nhs.uk/Accreditation>

In this issue: There have been several serious cases of hepatotoxicity – including six cases of liver failure – reported with use of the antidepressant **agomelatine**, since its marketing in 2009. Product information for agomelatine has been strengthened with new warnings and advice on the risk of hepatotoxicity. The existing recommendations to perform liver function tests at treatment initiation and during treatment have been extended to include testing when the dose is increased, in all patients receiving agomelatine. See article A1 for further information.

Also this month: clinicians should be aware that **intravenous hypotonic saline** (0.18% saline/4% glucose solution) is now contraindicated in children except under expert medical supervision in paediatric specialist settings – such as renal, liver, cardiac, high dependency and intensive care units. Use of this solution in children outside these conditions has resulted in several cases of hyponatraemia, including some that were fatal (see article A2).

Cases of severe symptomatic hypocalcaemia have been reported in patients receiving **denosumab** 120 mg or 60 mg. Some of these cases were fatal in patients receiving the 120 mg dose. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time during treatment. See article A3 for further information.

In the August 2012 edition of Drug Safety Update, we published updated advice on several drug interactions with **simvastatin**. In this month's issue, we focus on two of

these interacting drugs, amlodipine and diltiazem, and summarise the evidence for the new maximum dose recommendation for simvastatin (20 mg/day) when taken with these drugs (see article H1).

See our update on the continuing effective measures to manage the risk of misuse of **pseudoephedrine and ephedrine** in the manufacture of the class A drug methylamphetamine (article H2)

And finally: a new review has highlighted further evidence that diclofenac is associated with a cardiovascular risk that is higher than other non-selective **NSAIDs** and similar to selective COX-2 inhibitors (see article S1 for more information)

Priya Venkatesan, Editor
drugsafetyupdate@mhra.gsi.gov.uk

Drug safety advice

A1 Agomelatine (Valdoxan/ Thymanax): risk of dose-related hepatotoxicity and liver failure – updated warnings and monitoring guidance.

There have been several serious cases of hepatotoxicity reported with agomelatine (Valdoxan/Thymanax), including six reports worldwide of hepatic failure. The existing recommendations to perform liver function tests in all patients receiving agomelatine at treatment initiation and during treatment have been extended to include testing when the dose is increased.

Agomelatine should be immediately discontinued if patients present with symptoms or signs of potential liver injury, or if an increase in serum transaminases in liver function tests exceeds 3 times the upper limit of normal.

Patients should be informed of the symptoms of potential liver injury and advised to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.

Agomelatine is an antidepressant indicated for the treatment of major depressive episodes in adults. Agomelatine is a melatonin MT1 and MT2 receptor agonist, and antagonist at the serotonin 5-HT_{2C} receptor, thereby increasing levels of dopamine and noradrenaline in areas of the brain involved in mood control.

Following several reports of liver injury, including hepatic failure, all available data on elevated transaminases and hepatotoxicity with agomelatine use have been reviewed. In premarketing clinical studies (unpublished), increases in liver function parameters (>3 times the upper limit of normal [ULN]) were commonly reported [a rate of 1 in every 10 – 100 patients treated]. Serious hepatic reactions including hepatitis (cytolytic) and transaminase elevations >10 ULN were also seen. The rate of hepatic failure is rare – less than 1 in every 1000 patients treated.

See:
<http://www.medicines.org.uk/EMC/medicine/21830/SPC/Valdoxan/>

Due to these concerns, prescribers have been advised to monitor liver function frequently and warned about the risk of hepatitis and elevated transaminase levels >3 ULN since Valdoxan was first licensed in 2009.

The most recent review of hepatotoxicity found that the frequency of elevated transaminases > 3 ULN is dose-dependent, being higher in patients receiving 50 mg compared with 25 mg agomelatine (2.5 % versus 1.4 % respectively). For some patients treated in daily practice, hepatic reactions occurred following an increase in the dose. The median time to detection of hepatic reactions calculated from case reports is 50 days from treatment initiation.

A letter containing the new and existing advice on monitoring liver function was sent to healthcare professionals in October 2012, along with an educational guide to prescribing.

Further information:

BNF section 4.3 Antidepressant drugs
[link to:
<http://www.medicinescomplete.com/mc/bnf/current/PHP2440-agomelatine.htm>]

Advice for healthcare professionals:

- Prescribers should now perform liver function tests in all patients receiving agomelatine:
 - at initiation of treatment
 - at weeks 3, 6, 12, 24, and periodically thereafter
 - when increasing the dose of agomelatine (at the same time intervals as above) – this is new advice
 - whenever clinically indicated
- Any patient who develops increased serum transaminases should have their liver function tests repeated within 48 hours
- Agomelatine should be immediately discontinued if an increase in serum transaminases exceeds 3x ULN, or if patients present with symptoms or signs of potential liver injury, such as: dark urine; pale stools; jaundice; pain in the right upper abdomen; sustained new-onset and unexplained fatigue
- Patients should be informed of the symptoms of potential liver injury, and advised to stop taking agomelatine immediately and seek urgent medical advice if these symptoms appear.
- The balance of benefits and risks should be carefully considered before initiating treatment in patient with pre-treatment elevated transaminases levels or risk factors for hepatic injury, eg: obesity or being overweight, non-alcoholic fatty liver disease; substantial alcohol intake or use of concomitant medicines associated with risk of hepatic injury; diabetes. Extra vigilance is advised for such patients.
- Prescribers are reminded that agomelatine is contraindicated in patients with hepatic impairment, ie cirrhosis or active liver disease.

Article citation: Drug Safety Update Oct 2012 vol 6, issue 3: A1.

A2 Intravenous 0.18% saline/4% glucose solution ('hypotonic saline') in children: reports of fatal hyponatraemia – do not use in children aged 16 years or less, except in specialist settings under expert medical supervision

Four children have died of cerebral oedema caused by very low levels of serum sodium after receiving intravenous hypotonic saline (0.18% saline/4% glucose solution) in hospital. This solution is now contraindicated in children except under expert medical supervision in paediatric specialist settings – such as renal, cardiac, liver, high dependency and intensive care units

Intravenous hypotonic saline (0.18% saline/4% glucose infusion solution) is given to maintain normal fluid and electrolyte requirements, or to replenish substantial deficits or continuing losses.

Following the restart of a public inquiry primarily into the deaths of three children in the UK who died of cerebral oedema secondary to hyponatraemia after administration of intravenous hypotonic saline, the Commission on Human Medicines (CHM) has recently

reviewed all data on the benefits and risks of this solution when used in children.

References

- 1] Playfor et al (2004). Hypotonic intravenous solutions in children. *Expert Opin. Drug Saf* **3** (1); 67 – 73
- 2] Yung et al (2009). Randomized controlled trial of intravenous maintenance fluids. *J Paediatr Child Health* **49**: 9 – 14
- 3] Kannan et al (2010). Intravenous fluid regimen and hyponatraemia among children: a randomized controlled trial. *Paediatr Nephrol* **25**: 2303 – 2309
- 4] Drysdale et al (2010). The impact of the National Patient Safety Agency intravenous fluid alert on iatrogenic hyponatraemia in children. *Eur J Paediatr* **169** (7): 813 – 817

See:

National Patient Safety Agency (28th March 2007). Patient Safety Alert – [Reducing the risk of hyponatraemia when administering intravenous infusions to children](#)

Further information:

MHRA Public Assessment Report: Intravenous 0.18% saline/4% glucose infusion solution and the risk of hyponatraemia in children (link to: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON199554>)

BMJ E-Learning module: [Reducing the risk of hyponatraemia when administering intravenous fluids to children](#)

BNFC section 9.2.2.1: [Electrolytes and water](#)

Review outcome

There have been over 50 reported permanent neurological injuries or deaths in children worldwide as a result of iatrogenic hyponatraemia associated with the use of hypotonic intravenous fluids, often in previously healthy children undergoing routine elective surgery. In addition, several published studies and reviews have demonstrated hyponatraemia after administration of hypotonic intravenous fluids such as 0.18% saline/4% glucose^[1-4].

On the basis of the evidence from the review, the CHM concluded that the use of 0.18% saline/4% glucose should be contraindicated in all but a limited group of children treated by experts in paediatric specialist settings, such as renal, cardiac, liver, high dependency, and intensive care units.

Product information and packaging for intravenous 0.18% saline/4% glucose solutions is being updated with warnings on the risk of hyponatraemia.

The use of any hypotonic intravenous fluids puts children at a greater risk of developing hyponatraemia

Special care should be taken when giving intravenous infusions to infants and children as they are unable to regulate their fluid and electrolytes as effectively as adults. The tonicity and volume of intravenous solution needs to be carefully selected, based on the child's individual requirements.

A drop in sodium level is more likely to occur when hypotonic fluids are administered to children around surgery or during treatment of any of the following conditions: pain, anxiety, vomiting, fever, severe infection, low blood volume, breathing difficulties, cerebral infection. Hyponatraemia can cause headaches, seizures, tiredness, unconsciousness, cerebral oedema and may lead to death, and therefore children should be closely monitored while receiving intravenous fluid therapy.

Advice for healthcare professionals:

- Intravenous hypotonic saline (0.18% saline/4% glucose infusion) is now contraindicated in children aged 16 years or less except when initiated and maintained under expert medical supervision in paediatric specialist settings – such as renal, liver, cardiac, high dependency and intensive care units
- Remove 0.18% saline/4% glucose intravenous infusions from stock and general use in areas that treat children and ensure that suitable alternatives are available (in line with local guidelines). Restrict availability of 0.18% saline/4% glucose intravenous infusions to critical care and specialist wards – according to [National Patient Safety Agency's Alert 22](#).
- If hypotonic intravenous fluids do need to be prescribed to children (according to the strict conditions above), the child's individual clinical needs and possibility of increased anti-diuretic hormone secretion should be taken into account – fluid balance, plasma and urinary electrolyte concentrations must be carefully monitored during treatment.
- Acute symptomatic hyponatraemic encephalopathy is a medical emergency. Healthcare professionals should therefore be aware of and take prompt action if children receiving hypotonic intravenous fluids develop the signs and symptoms of hyponatraemia (headache, nausea, seizures, lethargy, coma, cerebral oedema).

Article citation: *Drug Safety Update Oct 2012 vol 6, issue 3: A2.*

A3 Denosumab: fatal cases of severe symptomatic hypocalcaemia, and risk of hypocalcaemia at any time during treatment – monitoring recommended

Cases of severe symptomatic hypocalcaemia have occurred in patients receiving denosumab 120 mg (Xgeva ▼) or 60 mg (Prolia ▼); some of these cases were fatal in those receiving the 120 mg dose.

Pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving the 120 mg dose unless hypercalcaemia is present. Although hypocalcaemia most commonly occurs within the first 6 months of treatment, it may occur at any time.

Denosumab 120 mg solution for injection (Xgeva ▼) is given once every 4 weeks for the prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumours.

Denosumab 60 mg solution for injection (Prolia ▼) is given once every 6 months for the treatment of osteoporosis in postmenopausal women at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk

Possible risk of fatal hypocalcaemia

Hypocalcaemia is a known risk with denosumab use, especially in patients with severe renal impairment (creatinine clearance <30 mL/min; estimated glomerular filtration rate [eGFR] 15 – 29 mL/min/1.73m²) or receiving dialysis. Severe symptomatic hypocalcaemia, including three fatal cases, has been reported in patients receiving denosumab 120 mg. Severe symptomatic hypocalcaemia has also been reported in patients at increased risk of hypocalcaemia receiving denosumab 60 mg.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation. Hypocalcaemia with denosumab most commonly occurs within the first 6 months of dosing, but it can occur at any time during treatment

Periodic monitoring of calcium levels (at the discretion of the prescriber) is recommended after use of denosumab in patients predisposed to hypocalcaemia, including those with severe renal impairment. In patients receiving 120 mg denosumab, supplementation of calcium and vitamin D is required unless hypercalcaemia is present; if hypocalcaemia occurs, additional calcium supplementation may be necessary.

See:

Letter sent to healthcare professionals in September 2012:

<http://www.mhra.gov.uk/home/groups/comms-ic/documents/websitesources/con185672.pdf>

A letter was sent to healthcare professionals in September 2012 regarding the updated product information for Xgeva ▼.

Further information:

BNF section 6.6: [Drugs affecting bone metabolism](#)

Advice for healthcare professionals:

The following precautions should be followed to minimise the risk of hypocalcaemia with denosumab:

Contraindications:

- Denosumab 120 mg (for cancer indications) should not be used in patients with severe, untreated hypocalcaemia
- Denosumab 60 mg (for osteoporosis indications) should not be used in patients with hypocalcaemia, regardless of severity*

** the contraindications vary between the two doses, because their indications are different.*

Warnings and recommendations:

- Pre-existing hypocalcaemia must be corrected prior to initiating denosumab, and supplementation of calcium and vitamin D is required in all patients receiving 120 mg denosumab unless hypercalcaemia is present.
- Adequate intake of calcium and vitamin D is important in all patients receiving 60 mg denosumab
- Patients with severe renal impairment (creatinine clearance <30 mL; eGFR 15 – 29 mL/min/1.73m²) or receiving dialysis are at greater risk of developing hypocalcaemia, and monitoring of calcium levels in these patients is recommended.

Article citation: *Drug Safety Update Oct 2012 vol 6, issue 3: A3.*

Hot topic

H1 Simvastatin: evidence supporting recent advice on dose limitations with concomitant amlodipine or diltiazem

See:

August 2012 Drug Safety Update advice:
<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON180637>

PEAG webpage:

<http://www.mhra.gov.uk/Committees/Medicinesadvisorybodies/CommissiononHumanMedicines/ExpertAdvisoryGroups/Pharmacovigilance/index.htm>

References:

1] Prueksaritanont T, Gorham LM, Ma B et al. In vitro metabolism of simvastatin in humans [sbtl]Identification of metabolizing enzymes and effect of the drug on hepatic P450s. *Drug Metab Dispos* 1997;25:1191-1199.

2] Katoh M, Nakajima M, Shimada N, Yamazaki H, Yokoi T. Inhibition of human cytochrome P450 enzymes by 1,4-dihydropyridine calcium antagonists: prediction of in vivo drug-drug interactions. *Eur J Clin Pharmacol* 2000;55:843-852.

Summary

In August 2012 we published advice that simvastatin is now contraindicated with concomitant use of certain medicines, such as ciclosporin, danazol, and gemfibrozil, and that the recommendations for the maximum dose of simvastatin have changed when used with a number of other medicines, including amlodipine and diltiazem. These changes were driven primarily by concerns about an increased risk of myopathy and/or rhabdomyolysis at higher plasma concentrations of simvastatin, which may result from such drug interactions.

Following further consideration by the Pharmacovigilance Expert Advisory Group (PEAG) of the Commission on Human Medicines, this article summarises the evidence underlying the new advice that the maximum recommended dose for simvastatin in conjunction with amlodipine and diltiazem is now 20 mg/day. The prescribed doses of amlodipine and diltiazem need not be changed.

Pharmacokinetic data

Simvastatin is metabolised through the CYP3A4 pathway. Concomitant use of CYP3A4 inhibitors has the potential to increase exposure to simvastatin.¹ Both amlodipine and diltiazem are substrates and inhibitors of CYP3A4^{2,3} and therefore increase the plasma concentration (AUC_{0-24h}) and maximum plasma concentration (C_{max}) of simvastatin when they are co-administered.

Studies have found that after 10 days of amlodipine (10 mg), the AUC_{0-24h} of simvastatin and simvastatic acid following a single dose of simvastatin 80 mg increased by 1.58- and 1.77- fold respectively, compared with that following a single dose of simvastatin 80 mg without prior amlodipine administration⁴. Use of amlodipine 5 mg with simvastatin 5 mg resulted in a proportionally smaller increase in simvastatin plasma concentration⁵.

Similarly, studies with diltiazem 120 mg twice daily for 10 days increased the AUC_{0-24h} of

3] Sutton D, Butler AM, Nadin L, Murray M. Role of CYP3A4 in human hepatic diltiazem N-demethylation: inhibition of CYP3A4 activity by oxidized diltiazem metabolites. *J Pharmacol Exp Ther* 1997;282:294-300

4] US product information for Zocor. http://www.merck.com/product/usa/pi_circulars/z/zocor/zocor_pi.pdf

a) Levels of creatine kinase are a marker for myopathy and other muscle symptoms

5] Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. *Hypertens Res* 2005;28:223-227.

6] Mousa O, Brater DC, Sunblad KJ, Hall SD. The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther* 2000;67:267-274.

7] FDA review (2011). http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/019766s077.pdf

8] Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. *The Lancet* 2003 June 14;361(9374):2005-16.

9] Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *The Lancet* 2010;376:1658-1669.

10] Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update *Fundam Clin Pharmacol* 2005;19:117-125.

simvastatin and simvastatic acid following a single dose of simvastatin 80 mg by 3.10 and 2.69 fold (compared with a single dose of simvastatin 80 mg without prior diltiazem treatment⁴). Increases in AUC as high as 5 fold with simvastatin 20mg and diltiazem (120mg twice daily) have been reported.⁶

Rates of myopathy in association with simvastatin

Although based on a small number of cases, the incidence of myopathy across a number of large trials increased when simvastatin 40 mg was administered with amlodipine. Similarly the incidence of muscle symptoms specifically associated with rises in creatine kinase (CK)^a with simvastatin 40 mg was between 2 – 3-fold greater in the presence of amlodipine compared with its absence⁷. The cumulative total of patients experiencing raised CK levels in the Heart Protection Study (HPS)⁸ was 1% for patients taking 40 mg simvastatin plus amlodipine, versus 0.36% for patients taking simvastatin alone. Consistent with this, the 5-year SEARCH clinical trial⁹ also demonstrated increases in the incidence of CK elevations with simvastatin 80 mg plus amlodipine which were not observed with simvastatin 20 mg plus amlodipine.

While the absolute incidence of myopathy is low, the prescribing of simvastatin 40 mg is high and amlodipine is a common co-medication. Additionally many patients at potential risk of muscle symptoms are excluded from clinical trials. Thus the relatively small increased risk imposed by amlodipine could translate into a significant number of additional adverse muscle effects in practice.

These observations are supported by reported cases of adverse muscle reactions. For example, in the FDA report⁷, there were 42 reports of rhabdomyolysis with simvastatin 40 mg plus amlodipine, compared with 20 reports with simvastatin 20 mg plus amlodipine. It must be remembered that such ratios are affected by many factors, such as relative prescribing rates.

In agreement with pharmacokinetic data, greater CK elevations were observed in SEARCH^{7,9} with simvastatin 80 mg when administered with diltiazem, compared with simvastatin 80 mg alone. This translated to a significant 3-fold increase in the incidence of myopathy when diltiazem was administered with high-dose simvastatin. The incidence of CK elevations was lower when diltiazem was administered with simvastatin 20 mg compared with 80 mg, and was similar to the incidence with simvastatin 20 mg alone.

Relative benefit of different simvastatin doses

The HPS trial demonstrated that simvastatin 40 mg has a clearly positive benefit-risk profile vs placebo,⁸ however, the additional benefit of simvastatin 40 mg versus 20 mg is anticipated to be smaller. As with all statins, most of the low-density lipoprotein (LDL)-lowering effect is apparent at lower doses of simvastatin (~75% of maximum effect is apparent with 20 mg) and only an additional 6% effect would be expected by doubling the dose from 20 mg to 40 mg¹⁰. SEARCH⁹ also failed to demonstrate any additional benefit of 80 mg vs 20 mg in terms of mortality and morbidity, a result which did not change with duration of treatment.

Alternative prescribing options are available for patients in whom the lower dose of simvastatin is not considered appropriate. There are currently no restrictions for co-administration of any of the other marketed statins with amlodipine. If switching to another statin is considered, the recommendations for monitoring or dose reduction for other interacting medicines should be taken into account.

In summary, the available evidence supports the recommendation that the maximum daily dose of simvastatin should not exceed 20 mg when co-administered with amlodipine or diltiazem:

- concomitant use of either amlodipine or diltiazem increases the exposure to simvastatin through CYP3A4 interactions

- the incidence of myopathy is increased with higher doses of simvastatin when co-administered with amlodipine or diltiazem, compared to the absence of amlodipine or diltiazem, or lower doses of simvastatin
- approximately 75% of the LDL-lowering effect is apparent at lower doses of simvastatin and only an additional 6% effect would be expected by doubling the dose from 20 mg to 40 mg¹⁰

See:

Patient article [link to: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON199556>]

Further information:

BNF section 2.12: Lipid-regulating drugs [link to: <http://www.medicinescomplete.com/mc/bnf/current/PHP1648-simvastatin-non-proprietary.htm#PHP1648-simvastatin-non-proprietary>]

In the absence of further evidence, the recommendation for a maximum daily dose of simvastatin of 20 mg applies with amlodipine at doses of both 10 mg and 5 mg.

Advice for prescribers

- The treatment of patients currently receiving concomitant simvastatin 40 mg and amlodipine or diltiazem should be reviewed at their next routine appointment. The maximum recommended dose of simvastatin co-administered with amlodipine or diltiazem is now 20 mg per day.
- A [patient article on the new information for simvastatin](#) is available to complement the consultation.

Article citation: Drug Safety Update Oct 2012 vol 6, issue 3: H1.

H2 Pseudoephedrine and ephedrine: update on managing risk of misuse

Pseudoephedrine and ephedrine are medicines used as nasal decongestants, which are available from pharmacies. Between 2007 and 2008, we introduced restrictions on their use because of concern that medicines containing these active substances could be used in the illicit manufacture of the Class A controlled drug methylamphetamine.

Sales restrictions

Since April 2008, after public consultation and following advice from the Commission on Human Medicines (CHM), the following sales restrictions have been in place in the UK to manage the risk of misuse of pseudoephedrine and ephedrine:

- It is illegal to sell or supply any product that contains more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a combination of products that between them add up to more than 720 mg pseudoephedrine or 180 mg ephedrine without a prescription
- It is illegal to sell or supply a product that contains pseudoephedrine and a product that contains ephedrine in one transaction
- Furthermore, the Royal Pharmaceutical Society advises that the sale and supply of these products must be made by a pharmacist or suitably trained pharmacy staff under the supervision of a pharmacist.

This information was first published in the October 2008 issue of Drug Safety Update.

See:

Royal Pharmaceutical Society website: <http://www.rpharms.com/home/home.asp>

October 2008 Drug Safety Update: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087857>

September 2009 Drug Safety Update: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON087910>

September 2010 Drug Safety Update: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON093847>

September 2011 Drug Safety Update: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON128959>

July 2011 Public Assessment Report: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/S>

The CHM has continually reviewed these measures and the impact on containing the potential problem of misuse (see Drug Safety Updates from September 2009, September 2010, and September 2011, and a Public Assessment Report published in July 2011).

Impact of restrictions: 2012 review

Between July 2011 and July 2012 there was one report in the UK of limited misuse, possibly linked to these medicines. The evidence suggests that the restrictions are continuing to help manage the risk of misuse. Further information is available in our Public

[afetywarningsandmessagesformedicines/CON126277](http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON126277)

July 2012 Public Assessment Report: <http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/CON199552>

Further information:

BNF section 3.10 Systemic nasal decongestants [link to: <http://www.medicinescomplete.com/mc/bnf/current/PHP2086-systemic-nasal-decongestants.htm>]

Royal Pharmaceutical Society website [link to: <http://www.rpharms.com/home/home.asp>]

Assessment Report: Pseudoephedrine and ephedrine: Managing the risk of misuse of medicines - July 2012 review.

Implementation of measures to regulate sales, together with the additional voluntary actions overseen by the profession, has made an important contribution to managing the risk of misuse of pseudoephedrine and ephedrine. The CHM recommended that existing levels of monitoring, education, and awareness measures by pharmacists should be maintained. We thank the pharmacy profession for their substantial contribution to managing the risk of misuse of these products.

Article citation: Drug Safety Update Mmm YYYY vol #, issue #: H#.

Stop press

S1 Non-steroidal anti-inflammatory drugs (NSAIDs): further evidence that the cardiovascular risk with diclofenac is higher than other non-selective NSAIDs and similar to the selective COX-2 inhibitors

See:

CHMP webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000094.jsp&mid=WC0b01ac0580028c79

PRAC webpage: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18

Further information:

Press release from the European Medicines Agency website [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/10/news_detail_001637.jsp&mid=WC0b01ac058004d5c1]

Previous advice on NSAIDs from Drug Safety Update February 2009 [link to: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088130>] and December 2007 [link to: <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084694>]

MHRA webpage on the cardiovascular safety of NSAIDs [link to: <http://www.mhra.gov.uk/Safetyinformation>]

A new review on the cardiovascular safety of NSAIDs has highlighted further evidence that diclofenac is associated with cardiovascular risks that are higher than the other non-selective NSAIDs, and similar to the selective COX-2 inhibitors. Naproxen and low-dose ibuprofen are still considered to have the most favourable cardiovascular safety profiles of all non-selective NSAIDs.

This review, by the European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP), evaluated all available data on this issue since the last review conducted in 2006.

The findings highlighted in this review are not new; an increase in risk of heart attack and stroke with some non-selective NSAIDs, such as diclofenac, particularly with long-term use of high doses and in patients who are already at high risk, is well recognised. Warnings have been included in the product information for healthcare professionals and patients, and in the BNF, for some years.

The need for any update to the existing treatment advice for diclofenac will now be assessed by the European Medicines Agency's Pharmacovigilance and Risk Assessment Committee (PRAC).

Healthcare professionals are reminded that, when prescribing NSAIDs, patients should use the lowest effective dose for the shortest time necessary to control symptoms. The patient's individual risk factors, including any history of cardiovascular and gastrointestinal illness, should also be taken into account.

[ation/Generalsafetyinformationandadvice/Product-specificinformationandadvice/Product-specificinformationandadvice-A-F/CardiovascularsafetyofCOX-2inhibitorsandnon-selectiveNSAIDs/index.htm\]](#)

BNF section 10.1 Drugs used in rheumatic diseases and gout [link to: <http://www.medicinescomplete.com/mc/bnf/current/PHP6435-voltarol-75-mg-sr.htm>]

Article citation: Drug Safety Update Oct 2012 vol 6, issue 3: S1.

Other information from the MHRA

See:

Link to antipsychotics learning module:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/Medicineslearningmodules/Antipsychoticslearningmodule/index.htm>

Link to opioids learning module:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/Medicineslearningmodules/Opioidslearningmodule/index.htm>

Link to SSRIs learning module:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/Medicineslearningmodules/Reducingmedicinerisk/SSRIlearningmodule/index.htm>

Education page:
<http://www.mhra.gov.uk/Conferences/LearningCentre/LearningCentre/index.htm>

O1 Learning about reducing medicines risk - Antipsychotics

We have recently launched a learning module on antipsychotics for clinical practitioners. The self-directed learning package outlines the key risks of this widely prescribed class of medicines. For each adverse effect, the module outlines:

- The main features of the adverse effect
- Factors that increase the risk
- How the risk can be reduced
- Specific treatment for the adverse effect

Self-assessment questions, together with full feedback, complement the learning material. Learners tell us that they greatly value the questions and the accompanying detailed feedback. Responding to comments on an earlier module on opioids we have increased the number of questions included in this module.

We have included a short online evaluation form at the end of the module—responses will help us tailor the modules to users' needs.

The antipsychotics learning module joins similar ones on selective serotonin reuptake inhibitors (SSRIs) and opioids.

The education page on our website lists other learning materials and gives information on obtaining continuing professional development (CPD) credits.

Article citation: Drug Safety Update Oct 2012 vol 6, issue 3: O1.