# 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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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 this issue: the risk of serious skin reactions induced by carbamazepine may be increased in patients of European descent or Japanese origin with the *HLA-A*3101* allele. However, there are currently insufficient data to support screening for this allele before starting carbamazepine treatment. Patients of European descent or Japanese origin who are known to be positive for this allele should only receive carbamazepine, oxcarbazepine or eslicarbazepine after careful consideration of the benefits and risks (see article A1)

Also this month: see article S1 for news on life-threatening and fatal reports of air embolism occurring with the use of sprayable fibrin sealants. Such events appear related to a higher-than-recommended spray pressure, or spraying too close to the tissue surface. Following a Europe-wide review, updated advice on the correct use of the fibrin sealant Evicel has been issued. Reviews of other fibrin sealants are being finalised and updated advice on these will be provided very soon.

A European review of the safety of codeine-containing pain-relief medicines used in children has been initiated. The review was triggered by very rare, non-UK reports of fatalities, and life-threatening respiratory depression, in children who had been given codeine for post-operative pain following tonsillectomy or adenoidectomy. These children were found to be ultra-rapid or extensive codeine metabolisers. See article S2 for more information.

Finally, try our end-of-year quiz to test yourself on some of the key safety advice provided in 2012. You may also be able to use the completed quiz to claim Continuing Professional Development points (see article O1).

We wish all of our readers a very happy New Year.

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# Drug safety advice

## A1 **Carbamazepine, oxcarbazepine and eslicarbazepine: serious skin reactions associated with the *HLA-A* 3101* allele**

The risk of serious skin-related adverse drug reactions, including Stevens-Johnson syndrome, occurring with carbamazepine may be increased in the presence of the *HLA-A*3101* allele in patients of European descent or Japanese origin. However, there are currently insufficient data to support screening for this allele before starting carbamazepine treatment. Patients of European descent or Japanese origin who are known to be positive for this allele should only receive carbamazepine, oxcarbazepine or eslicarbazepine after careful consideration of the benefits and risks.

Carbamazepine (Tegretol) is an antiepileptic drug that is indicated for the treatment of generalised tonic clonic seizures. Carbamazepine is also licensed to treat the paroxysmal pain of trigeminal neuralgia and for the prophylaxis of manic-depressive psychosis in patients unresponsive to lithium therapy.

Oxcarbazepine (Trileptal) is indicated for the treatment of partial seizures with or without secondary generalisation and is closely structurally related to carbamazepine.

Eslicarbazepine (Zebinix) is the active metabolite of oxcarbazepine and indicated as adjunctive therapy in adults with partial onset seizures with or without secondary generalisation.

It is well-recognised that severe, potentially life-threatening, skin-related adverse drug reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can occur rarely in association with carbamazepine. The frequency of such skin reactions has been estimated to be about one to six cases per 10 000 new users of carbamazepine in the USA and Europe.

See:
April 2008 Drug Safety Update [link to: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON084888 ]

Carbamazepine Summary of Product Characteristics [link to: http://www.medicines.org.uk/EMC/medicine/1328/SPC/Tegretol+Tablets+100mg%2c+200mg%2c+400mg/]

Human leukocyte antigens (HLA) are involved in some drug-specific abnormal immune responses including SJS and TEN), and the HLA allele *HLA-B*1502* is known to be highly associated with carbamazepine-induced SJS and TEN in certain Asian populations[1,2]. We informed you in 2008 of the association between carbamazepine-induced SJS and *HLA-B*1502* in patients of Han Chinese, Hong Kong Chinese and Thai origin, with advice to screen these individuals for *HLA-B*1502* before starting carbamazepine treatment. Since 2008, new study findings have become available suggesting an association with serious skin-related adverse drug reactions, including Stevens-Johnson syndrome, and *HLA-B*1502* in other Asian populations [3,4]. In addition, the clinical utility of *HLA-B*1502* screening before starting carbamazepine treatment has recently been shown in Han Chinese individuals [5].

More recently, a new genetic marker, *HLA-A*3101*, has been identified in Japanese individuals and individuals of European descent for serious carbamazepine-induced cutaneous adverse drug reactions such as SJS, TEN, and drug rash with eosinophilia (DRESS), and less severe reactions such as acute generalised exanthematous pustulosis (AGEP) and maculopapular rash[6,7].

The frequency of *HLA-A*3101* varies widely between ethnic populations, with a prevalence of 2 – 5% in European populations and approximately 10% in the Japanese population. The presence of the *HLA-A*3101* allele may increase the risk for carbamazepine-induced cutaneous reactions (mostly less severe reactions) from 5% to 26% in patients of European descent. Its absence may reduce the risk from 5% to 3.8% in patients of European descent. However, the sensitivity of the *HLA-A 3101* test for SJS in European and Japanese patients is relatively low (5/12 cases [42%] in

References:
1] Phillips EJ et al. Drug hypersensitivity: pharmacogenomics and clinical syndromes. *J Allergy Clin Immunol*. 2011 Mar; **127**(3 Suppl): S60 – 66.

2] Mushirada T, Nakamura Y. Personalizing carbamazepine therapy. *Genome Med*. 2011 May; **3**(5): 2.

3] Mehta TY et al. Association of HLA-B1502 allele and carbamazepine–induced Stevens-

Johnson Syndrome among Indians. *Indian J Dermatol Venereol Leprol* 2009;**75**: 579 – 582

4] Chang CC et al. Association of the HLA-B1502 allele with carbamazepine-induced toxic epidermal necrolysis and Stevens-Johnson Syndrome in the multi-ethnic Malaysian population. *Int J Dermatol* 2011; **50**(2):221 – 224

5] Chen P et al. Carbamazepine-induced toxic effects and HLA-B1502 screening in Taiwan. *N Eng J Med* 2011; **364**: 1126 – 1133.

6] Ozeki T et al. Genome-wide association study identifies HLA-A3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet* 2011; **20**(5): 1034 – 1041

7] McCormack M et al. HLA-A3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *N Eng J Med* 2011; 364: 1134 – 1143

**Further information:**

BNF section 4.8 Antiepileptic drugs [link to: http://www.medicinescomplete.com/mc/bnf/current/PHP2898-control-of-the-epilepsies.htm]

patients of European descent and 5/6 cases [83%] in Japanese patients) when compared to the *HLA-B*1502* test for SJS (where sensitivity approaches 100%)[7]. It is also noteworthy that the number of patients included in the *HLA-A*3101* studies was small and there are no prospective studies on the clinical utility of *HLA-A* 3101* testing in any population.

Currently there are insufficient data supporting a recommendation for *HLA-A*3101* screening before starting carbamazepine or chemically-related medicines. If patients of European descent or Japanese origin are known to be positive for *HLA-A*3101*, the use of carbamazepine or chemically related compounds may be considered, but only after careful consideration of the expected benefits of treatment and the increased risk of serious skin conditions.

Data supporting an association of *HLA-A *3101* with oxcarbazepine and eslicarbazepine-induced skin reactions are very limited but due to their close structural relationship with carbamazepine and reports of hypersensitivity with cross reactivity, the advice has been extended to cover not only carbamazepine but these two structurally related products.

Advice for healthcare professionals:

- Carbamazepine is associated with a risk of potentially life-threatening skin-related adverse drug reactions, including Stevens-Johnson syndrome. If signs and symptoms suggestive of severe skin reactions appear, treatment should be withdrawn at once and alternative treatment should be considered
- The presence of the *HLA-A*3101* allele may increase the risk for carbamazepine-induced skin reactions in patients of European descent or Japanese origin
- If patients of European descent or Japanese origin are known to be positive for HLA A*3101 they should only receive carbamazepine, oxcarbazepine, or eslicarbazepine after careful consideration of the benefits and risks

*Article citation: Drug Safety Update December 2012 vol 6, issue 5: A1.*

## S1 **Evicel fibrin sealant spray application: life-threatening and fatal air embolism – updated advice on minimising risk**

Fibrin sealants (also known as tissue adhesives or glues) are used in a wide range of surgical procedures to rapidly arrest bleeding and assist in subsequent wound healing. They are applied either by dripping or spraying onto the tissue surface.

There have been reports of life-threatening and fatal cases of air embolism occurring in association with the use of spray devices employing pressure regulators to administer fibrin sealants. Such events appear to be related to the use of the spray device at higher-than-recommended pressures, and/or in closer-than-recommended proximity to the tissue surface. We first informed you of this risk in October 2010.

Worldwide, a total of six reports have been received of life-threatening or fatal air embolism with the sprayable fibrin sealants Evicel (5 reports) and Tisseel (1 report), and a further four reports in association with Quixil, a sprayable fibrin sealant which is no longer available in the UK.

Further information:

Press release from the European Medicines Agency [link to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2012/11/news_detail_001659.jsp&mid=WC0b01ac058004d5c1]

Following a recent European review of the benefits and risks of these products, a number of recommendations have been made for Evicel to minimise the risk of air embolism when this medicine is applied as a spray during surgery.

Advice for healthcare professionals:

- For spray application of Evicel using a pressure regulator device, only $CO_2$ gas should be used (not pressurised air)
- When spraying Evicel in open-wound surgery, the maximum pressure should be 1.7 bar (25 psi). The product should be sprayed at least 10 cm or more from the tissue surface
- When spraying Evicel in laparoscopic surgery, the maximum pressure should be 1.4 bar (20 psi). The product should be sprayed at least 4 cm or more from the tissue surface, and only used if the spray distance can be accurately judged
- Do not use Evicel in other endoscopic procedures
- Prior to applying Evicel, the surface area of the wound should be dried using standard techniques (eg, intermittent application of compresses, swabs, and use of suction devices)
- Closely monitor blood pressure, heart rate, oxygen saturation and end-tidal $CO_2$ when spraying Evicel, because of the possibility of air embolism
- Please report suspected adverse reactions with fibrin sealants through the Yellow Card Scheme at www.mhra.gov.uk/yellowcard

Reviews of other fibrin sealants (Tisseel Ready for use solution for sealant, Tisseel Lyo, Artiss solution for sealant, deep frozen) are being finalised, and we will provide updated advice very soon.

*Article citation: Drug Safety Update December 2012 vol 6, issue 5: S1.*

## S2 **Codeine-containing pain relief in children: safety review initiated following post-surgical fatalities in ultra-rapid metabolisers**

Codeine is a widely used opioid analgesic and is sometimes used for post-operative pain relief in children.

See:
European review of codeine-containing pain relief in children [link to: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine_containing_medicinal_products/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f]

A European review of the safety of medicines containing codeine licensed for pain relief in children (aged 0-18 years) was started in October 2012.

The ongoing review was triggered by recent concerns that there is an increased risk of morphine toxicity when certain susceptible children are given codeine for post-operative pain after surgery. These concerns follow the reporting of three fatalities, and one life-threatening case of respiratory depression in children given codeine after tonsillectomy or adenoidectomy in the treatment of obstructive sleep apnoea [1,2]. The US Food and Drug Administration (FDA) have also communicated on this issue.

FDA communication [link to: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm315601.htm]

The risk of post-surgery respiratory depression in certain susceptible children following codeine use may be due to their genetically determined rate of codeine metabolism. Codeine is metabolised to morphine via the cytochrome P450 enzyme CYP2D6 and genetic differences in the expression of this enzyme, according to racial or ethnic group, determine the extent to which codeine is metabolised. A faster metabolism results in higher-than-normal blood levels of morphine which can lead to toxic effects such as breathing difficulties. Up to approximately 6.5% of Caucasians may be ultra-rapid metabolisers of codeine (the frequency varies between countries).

The three fatal cases following post-surgical codeine occurred in children who had evidence of being ultra-rapid metabolisers of codeine; the life-threatening case of respiratory depression occurred in a child who was defined as an extensive metaboliser [1,2].

BNFc section 4.7.2 Opioid analgesics [link to: http://www.medicinescomplete.com/mc/bnfc/current/PHP12346-codeine-phosphate.htm#PHP12349]

The BNF for Children contains a note for caution with regard to variable metabolism for codeine and the marked increase in side-effects that can occur with rapid metabolism.

The European review will evaluate the impact of the new information on the balance of benefits and risks of codeine-containing medicines when used for pain relief in children. The outcome of the review will be communicated when available.

### Advice for healthcare professionals

- Clinicians should remain aware that patients may respond differently to codeine. Those caring for patients taking codeine should be advised to seek professional help if symptoms of toxicity occur
- Symptoms of codeine toxicity include reduced levels of consciousness, lack of appetite, somnolence, constipation, respiratory depression, ‘pin-point’ pupils, nausea and vomiting

*Article citation: Drug Safety Update December 2012 vol 6, issue 5: S2.*

# End-of-year quiz

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

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

The answers are given at the bottom of the quiz.

Some articles in Drug Safety Update are more relevant for some healthcare professionals than for others, so feel free to attempt only the questions related to your specialty.

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

**1** Paracetamol overdose is sometimes treated with acetylcysteine (Parvolex and generics). What approach to treatment should always be taken when there is doubt over the timing of paracetamol ingestion?

**2** Inadvertent switching between oral tacrolimus products has been associated with reports of toxicity and graft rejection. How should oral tacrolimus prescriptions be written in order to minimise this risk?

**3** What adverse effect associated with the antibacterial chlorhexidine should healthcare professionals be aware of, and prepared for?

**4** Which electrolyte disturbance can occur with long-term proton pump inhibitor (PPI) treatment? Monitoring for this electrolyte disturbance should be considered especially in patients taking which other drugs?

**5** Acute pancreatitis has been reported with use of all drugs in which class of drugs for the treatment of type 2 diabetes mellitus? Name two members of this class of drugs?

**6** The combination of aliskiren with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) is not recommended for any patient groups. Why? In which patient groups is the combination absolutely contraindicated?

**7** What is the new maximum recommended dose of simvastatin when used with amlodipine or diltiazem? Why has this limitation been introduced?

**8** Which non-selective non-steroidal anti-inflammatory drug (NSAID) has a cardiovascular risk that is higher than other non-selective NSAIDs, and similar to the selective COX-2 inhibitors?

**9** What risk with ondansetron has resulted in a new maximum single intravenous dose for the management of chemotherapy-induced nausea and vomiting (CINV) in adults? What is the new maximum dose in this setting?

**10** How can you report a suspected adverse drug reaction?

## Quiz answers

**1** Always give acetylcysteine without delay.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON185624

**2** Prescribe and dispense oral tacrolimus products by brand name only.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON155756

**3** Hypersensitivity, including generalised allergic reactions and anaphylactic shock.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON140701

**4** Hypomagnesaemia. Healthcare professionals should consider measuring magnesium levels before starting PPI treatment and repeat measurements periodically during prolonged treatment, especially in those who will take a PPI concomitantly with digoxin or drugs that may cause hypomagnesaemia (eg, diuretics).

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON149774

**5** The dipeptidylpeptidase-4 (DPP-4) inhibitor class of antidiabetic agents ('gliptins'). Drugs in this class include Onglyza▼ (saxagliptin), Trajenta▼ (linagliptin), Galvus▼ (vildagliptin) and Januvia (sitagliptin). A number of fixed-dose combination tablets containing a DDP-4 inhibitor with metformin are also available, including Eucreas▼ (vildagliptin) and Janumet (sitagliptin).

See: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON185628]

**6** Following concerns raised in the 'ALTITUDE' study, a review of all data confirmed a risk of adverse outcomes (hypotension, syncope, stroke, hyperkalaemia, and changes in renal function including acute renal failure) when aliskiren is combined with ACE inhibitors or ARBs. This combination is not recommended for any patient and is contraindicated in patients with type I or type II diabetes; and non-diabetic patients with impaired renal function - eGFR <60 mL/min per 1.73 $m^2$

See: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON146526]

**7** The maximum recommended dose for simvastatin in conjunction with amlodipine or diltiazem is now 20 mg/day. 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 combinations.

See: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON180637] and: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199561]

**8** Diclofenac is associated with cardiovascular risks that are higher than the other non-selective NSAIDs, and similar to the selective COX-2 inhibitors.

See: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON199570 ]

**9** There is a greater risk of prolongation of the electrocardiographic-corrected QT interval (QTc), a known side effect of ondansetron, when it is used at the higher doses previously authorised for CINV. The new maximum dose in this setting is 16 mg infused over at least 15 minutes

See: http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON180635 ]

**10** Report suspected adverse drug reactions via the Yellow Card Scheme—the simplest way to report is via www.mhra.gov.uk/yellowcard

*Article citation: Drug Safety Update December 2012 vol 6, issue 5: O1.*