Drug Safety Update

MHRA

Latest advice for medicines users

The monthly newsletter from the **MHRA** and its independent advisor the **Commission on Human Medicines**

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Contents

The **MHRA** 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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Tolvaptan (Samsca▼) is a treatment for adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH). Drug-induced liver injury has been observed in clinical trials investigating potential use in patients with autosomal dominant polycystic kidney disease (ADPKD, an unlicensed indication). The possibility that patients with SIADH treated with tolvaptan for hyponatraemia are potentially at increased risk of liver injury cannot be excluded. Therefore, liver-function tests should be done in patients taking tolvaptan who report signs or symptoms that suggest liver injury. Treatment with tolvaptan should be stopped during investigations into the probable cause of liver injury and patients treated with alternative appropriate treatment (see article A1).

An ongoing study has shown an increased risk of haematological second primary malignancies (acute myeloid leukaemia and myelodysplastic syndromes) in patients with newly diagnosed multiple myeloma who were receiving melphalan, prednisone, and thalidomide, compared with patients treated with lenalidomide plus dexamethasone. Before starting thalidomide treatment in combination with melphalan and prednisone, healthcare professionals should take into account both the likely benefit expected from thalidomide and the risk of acute myeloid leukaemia and myelodysplastic syndromes (see article A2).

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

Drug safety advice

A1 Tolvaptan (Samsca▼): risk of liver injury—liver-function testing recommended in patients with symptoms that may indicate liver injury

Drug-induced liver injury has been observed in clinical trials investigating potential use in patients with autosomal dominant polycystic kidney disease (ADPKD, an unlicensed indication) at higher doses than those for the approved indication and in long-term use.

Liver-function tests should be done in patients taking tolvaptan who report signs or symptoms that suggest liver injury. Treatment with tolvaptan should be stopped during investigations into the probable cause of liver injury and patients treated with alternative appropriate treatment

Tolvaptan (Samsca▼) is a selective vasopressin V2-receptor antagonist licensed only for the treatment of adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH) at a dose of 15–60 mg once a day.

Tolvaptan increases urine production without affecting sodium excretion, thereby raising serum sodium and lowering the amount of water in the body.

A clinical trial[1] in the USA investigating the potential use of tolvaptan in about 1400 patients with autosomal dominant polycystic kidney disease (ADPKD, an unlicensed indication) has identified an increased risk of serious liver injury in adults assigned 120 mg tolvaptan daily (ie, twice the maximum recommended daily dose in the licensed indication) compared with placebo.

1 Torres VE, et al. *N Engl J Med* 2012; **367:** 2407–18.

In the ADPKD population, clinically significant increases in both serum alanine aminotransferase (ALT, >3 times the upper limit of normal [ULN]) and total bilirubin (>2 times ULN) were observed in three patients assigned tolvaptan and no patients assigned placebo. Furthermore, there were significant elevations to >3 times ULN for ALT (4.4% for tolvaptan *vs* 1.0% for placebo) and for serum aspartate aminotransferase (AST, 3.1% *vs* 0.8%, respectively). Most of the liver enzyme abnormalities were observed during the first 18 months of treatment. The elevations gradually improved after discontinuation of tolvaptan and were not associated with fulminant liver failure, or with permanent liver injury or dysfunction.

Other clinical trials of tolvaptan for hyponatraemia, including those supporting the European-approved indication, did not show an increased incidence of liver injury compared with placebo. However, patients with hyponatraemia treated with tolvaptan were more likely to have elevations in total bilirubin or ALT than placebo. These data cannot exclude the possibility that patients with SIADH treated with tolvaptan for hyponatraemia are potentially at increased risk of liver injury.

Advice for healthcare professionals:

- Tolvaptan is licensed only for the treatment of adults with hyponatraemia secondary to inappropriate antidiuretic hormone secretion (SIADH) at a dose of 15–60 mg once a day
- Patients taking tolvaptan who report symptoms that may indicate liver injury should receive prompt liver-function testing. These symptoms include fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice

Continues…

Further information

BNF section 6.5.2 Posterior pituitary hormones and antagonists (http://www.bnf.org/bnf/search.htm?q=tolvaptan)

- Patients with liver enzyme abnormalities (such as elevations of ALT, AST, or bilirubin) should be investigated to exclude significant hepatotoxicity
- Prescribers should stop tolvaptan treatment in patients if liver injury is suspected and use alternative appropriate treatment. Tolvaptan should not be restarted in patients, unless the cause of the observed liver injury is definitively established to be unrelated to tolvaptan treatment
- Suspected hepatic adverse drug reactions to tolvaptan should be reported to us on a Yellow Card (www.mhra.gov.uk/yellowcard)

Article citation: Drug Safety Update May 2013 vol 6, issue 10: A1.

A2 Thalidomide: risk of second primary malignancies

Patients treated with thalidomide have an increased risk of haematological second primary malignancies (acute myeloid leukaemia and myelodysplastic syndromes). Healthcare professionals should consider this risk when deciding whether to treat patients with thalidomide, and should monitor for the occurrence of these conditions

Thalidomide (Thalidomide Celgene) is licensed for use in combination with melphalan and prednisone as first-line treatment for patients with untreated multiple myeloma who are age 65 years or older, or those who are ineligible for high-dose chemotherapy. Thalidomide is an immunomodulatory agent, which has antineoplastic, antiangiogenic, and proerythropoietic properties.

See http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON134927

In November 2011, we published information about the risk of development of second primary malignancies with lenalidomide (a structural analogue of thalidomide) in patients treated for myeloma. The risk of second primary malignancies associated with thalidomide was investigated because of the similarities between thalidomide and lenalidomide.

The data show an increased risk of haematological second primary malignancies (acute myeloid leukaemia and myelodysplastic syndromes) in an ongoing study of patients with newly diagnosed multiple myeloma who were receiving melphalan, prednisone, and thalidomide, compared with patients treated with lenalidomide plus dexamethasone. The risk of acute myeloid leukaemia or myelodysplastic syndromes with thalidomide increased from approximately 2% after 2 years to 4% after 3 years.

Further information

Letter sent to healthcare professionals, April 2013 (see

http://www.mhra.gov.uk/Safetyinformation/Safetywarningsalertsandrecalls/Safetywarningsandmessagesformedicines/Monthlylistsofinformationforhealthcareprofessionalsonthesafetyofmedicines/CON270715)

BNF section 8.2.4 Other immunomodulating drugs: http://www.bnf.org/bnf/search.htm?q=thalidomide

Advice for healthcare professionals:

- Before starting thalidomide treatment in combination with melphalan and prednisone, take into account both the likely benefit expected from thalidomide and the risk of acute myeloid leukaemia and myelodysplastic syndromes
- Carefully evaluate patients before and during treatment using standard cancer screening and provide appropriate treatment

Article citation: Drug Safety Update May 2013 vol 6, issue 10: A2.

Bulletin continues…

Yellow Card Scheme update

Y1 **Black Triangle (▼) medicines now part of an EU-wide scheme: remember to report any suspected adverse reactions**

Although the Black Triangle (▼) has been in place in the UK for many years to signify medicines that are subject to intensive monitoring, it will now also be used in all EU countries and this list of medicines has been agreed Europe-wide. Throughout Europe, this scheme is known as 'additional monitoring'.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of a medicine is important for continued monitoring of the balance of benefits and risks. The same monitoring methods are used across the EU so that information gathered in individual countries can be shared. This provides a wealth of knowledge for regulators and enables us to act quickly to protect public health, for example by providing warnings to healthcare professionals and patients, or restricting the way a medicine is used.

If a medicine carries a Black Triangle (▼), this means that it is subject to intensive monitoring. We are particularly interested in hearing about any suspected adverse reactions associated with these medicines. You can report online at www.mhra.gov.uk/yellowcard

A Black Triangle will be assigned to a medicine if:

- it contains a new active substance; new medicines or vaccines authorised on or after January 2011 are assigned a Black Triangle
- it is a biological medicine (eg, a vaccine or a medicine derived from plasma)
- it has been given a 'conditional approval' (enabling medicines to reach patients with unmet medical needs earlier than might otherwise be the case while ensuring that additional data on a product are generated, submitted, assessed, and acted on)
- it is approved 'under exceptional circumstances' (where the company is unable to provide comprehensive data for safety and efficacy under normal conditions of use because, for example, the indication is so rare)
- the company that markets the medicine is required to carry out additional studies (eg, to obtain data on long-term use or a rare side effect seen in clinical trials)

See http://www.mhra.gov.uk/Safetyinformation/Reportingsafetyproblems/Reportingsuspectedadversedrugreactions/informationforhealthcareprofessionals/BlackTriangleScheme/index.htm#10

The up-to-date list of Black Triangle medicines is published every month on the MHRA website.

Black Triangle symbol in product information

The Black Triangle symbol will continue to appear in the Summaries of Product Characteristics and in advertising for the relevant medicines.

For the first time in EU countries, the Black Triangle will start appearing in the Patient Information Leaflets of the relevant medicines from the autumn of 2013. It is important that if patients ask you about the Black Triangle symbol that you explain that any suspected side effects should be reported on a Yellow Card, and that they should speak to a healthcare provider if they have any concerns about a medicine. Furthermore, it is also important that patients, consumers, and carers understand that the Black Triangle does not indicate that the medicines are unsafe—the symbol is simply a way of helping to ensure that new safety information can be quickly identified, and they can help by reporting any side effects.

It is important to note that there may be a delay between the decision to add or remove a medicine from the Black Triangle list and the time when its updated product information (displaying the Black Triangle or not, respectively) comes into circulation. This is because it takes some time for the updated product information to gradually replace older stock already on the EU market.

Article continues….

See http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs/index.htm or EMA website if holds a Europe-wide license http://www.ema.europa.eu/ema/

Remember that up-to-date product information (SPCs and PILs) is available on the MHRA website.

The Black Triangle symbol is also displayed next to relevant medicines in the British National Formulary (http://www.bnf.org/bnf/index.htm), British National Formulary for Children, and in the Monthly Index of Medical Specialties (MIMS http://www.mims.co.uk/).

Article citation: Drug Safety Update May 2013 vol 6, issue 10: Y1.

Stop press

S1 **Liothyronine 20 microgram tablets: continuity of supply and potential need for patient monitoring**

There has been a recent interruption to the supply of liothyronine 20 microgram tablets from Amdipharm Mercury.

As a result of this current unavailability, patients taking this medicine may have had their prescription filled by an unlicensed product (imported from the EU) under the direct personal responsibility of a prescriber. The interchangeability of Amdipharm Mercury liothyronine tablets with liothyronine tablets that are not currently licensed in the UK cannot be assured because they may not be bioequivalent.

Advice for healthcare professionals and patients:

- Prescribers should be alert to the possibility that a change in a patient's symptoms and thyroid-stimulating hormone (TSH) status may be attributed to switching between liothyronine 20 microgram tablets from Amdipharm Mercury and another product
- Patients who experience a significant change in symptoms should have their TSH status reviewed and their dose of liothyronine adjusted accordingly
- The following patients may be particularly susceptible to changes in bioavailability of liothyronine and may require particularly close monitoring:
    - Pregnant women, throughout pregnancy but especially in the first trimester
    - Those with heart disease

  These patients who have been prescribed an alternative, unlicensed product should be contacted and given an early appointment for a clinical review and blood test
- In the small number of patients prescribed liothyronine long term (usually in combination with levothyroxine), thyroid function tests should be repeated 1–2 months after any change in preparation to ensure the target TSH has been maintained

Article citation: Drug Safety Update May 2013 vol 6, issue 10: S1.