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Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Change in the pregnancy category for topiramate

The TGA is advising health professionals of the change in the pregnancy category for topiramate-containing products from B3 to D.

Topiramate is indicated for the treatment of epilepsy in adults and children aged two years and over, and for the prophylaxis of migraine headache in adults. There are also reports of off-label use of topiramate to assist with weight loss.[1]

The Australian Product Information (PI) already contains warnings regarding the potential effects on the fetus, and recommends that women considering using topiramate receive pregnancy counselling to ensure they are aware of the potential risks to the fetus.

In May 2011, the US Food and Drug Administration advised that there were new data from the North American Antiepileptic Drug Pregnancy Registry that showed an increased risk for the development of cleft lip and/or palate in infants exposed to topiramate during the first trimester of pregnancy.

Following a review of these data, the TGA has changed the pregnancy category for topiramate products from Australian Pregnancy Category B3 to Category D.

Category D medicines are defined as 'Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.'

The PI has been updated to reflect this change and to incorporate this new data in the Precautions section.[2] More information about prescribing medicines in pregnancy is available from the TGA website.[3]

Information for health professionals

Health professionals should advise women of childbearing age of the increased risk for oral clefts when topiramate is used during pregnancy.

Topiramate should be used in pregnancy only if the potential benefits outweigh the potential risks to the fetus. Consideration should be given to prescribing other medicines that have a lower risk of adverse birth outcomes in women of childbearing age.

If a decision is made to prescribe topiramate, health professionals should recommend an appropriate method of contraception for women. In doing so, it should be borne in mind that there is the potential for decreased contraceptive efficacy when using topiramate with estrogen-containing contraceptives.[2]

REFERENCES

1. Topiramate – adverse events associated with use to assist with weight loss. Safety advisory. Therapeutic Goods Administration. 2011 Nov.
2. Topamax Product Information. Janssen-Cilag Pty Ltd. 2011 Nov.
3. Prescribing medicines in pregnancy database. Therapeutic Goods Administration. 2011 May.

Medicines Safety Update is the medicines safety bulletin of the Therapeutic Goods Administration (TGA)

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Use of 2012 seasonal influenza vaccines in children

The TGA advises health professionals that for the 2012 influenza season, there are four influenza vaccines registered for use in children from the age of 6 months – Agrippal, Fluarix, Influvac and Vaxigrip. An additional influenza vaccine, Fluvax, is registered for use in children from the age of 5 years. However, health professionals are advised of special precautions which apply to the use of Fluvax in children aged between 5 and 9 years of age.

During the 2010 influenza season an excess number of febrile reactions and febrile convulsions occurred in children under 5 years of age following immunisation with one of the registered seasonal trivalent influenza vaccines, Fluvax.[1] Consequently, in 2011 the TGA recommended that only Influvac and Vaxigrip vaccines be used in children aged between 6 months and 5 years. These vaccines had been used in Australian children in 2010 and had not been shown to be associated with an increased rate of fever or febrile reactions. Two additional vaccines, Agrippal and Fluarix, had not been supplied in Australia in 2010, and the sponsors had been unable to establish active surveillance to monitor the safety of their vaccines in paediatric populations for the 2011 season. Therefore, the TGA recommended against the use of Agrippal and Fluarix in children under the age of 9 years in 2011.

Recommendations for use in 2012

The sponsors of Agrippal and Fluarix have submitted additional data to the TGA to support the safety of their vaccines in children. The data submitted included the experience with their vaccines in the:

- 2011 Southern Hemisphere winter; and
- 2011/2012 Northern Hemisphere winter.

Following evaluation, the TGA has found these data raise no safety concerns related to fever or febrile convulsions in children who received either vaccine. The TGA now considers that Agrippal and Fluarix may be used in children from the age of 6 months, noting there has been no change to the strains in the vaccine to affect the safety profile of the vaccines in 2012.

Those providing immunisations should note that special precautions apply to the use of Fluvax in children between 5 and 9 years of age. Febrile events have been observed in children aged 5 to 9 years following immunisation with Fluvax. Therefore, in this age group, a decision to vaccinate with the 2012 Fluvax vaccine should be based on careful consideration of potential benefits and risks in the individual.

The TGA has registered five vaccines for use in children for the 2012 influenza season, with the indications shown in the following table.

An additional vaccine, Intanza (Sanofi Pasteur), is only registered for use in adults aged 18 to 59 years.

For further information on individual vaccines, please refer to the relevant Product Information document.

Vaccine	Sponsor	Approved indication
Agrippal	Novartis	6 months and over
Fluarix	GSK	6 months and over
Influvac *	Abbott	6 months and over
Vaxigrip *	Sanofi Pasteur	6 months and over
Fluvax †	CSL	5 years and over

* These vaccines also have a paediatric 0.25 mL ('junior') presentation registered for use in children aged 6–35 months

† Febrile events have been observed in children aged 5–9 years following immunisation with Fluvax. Therefore, in this age group a decision to vaccinate with the 2012 Fluvax vaccine should be based on careful consideration of potential benefits and risks in the individual.

Reporting of adverse events following influenza vaccine

Health professionals are encouraged to report all adverse events associated with influenza vaccination in patients of any age to the TGA or through the current requirements in their State or Territory. All reports contribute to the TGA's ongoing monitoring of the safety of influenza vaccines.

REFERENCE

1. Investigation into febrile reactions in young children following 2010 seasonal trivalent influenza vaccination. Status report as at 2 July 2010 (updated 24 September 2010). Canberra: Therapeutic Goods Administration; 2010.

MEDICINES SAFETY UPDATE

Dasatinib (Sprycel) and pulmonary arterial hypertension

Pulmonary arterial hypertension is known to be a serious but rare adverse event associated with dasatinib therapy. Physicians and general practitioners with patients taking dasatinib are urged to be vigilant for this adverse effect and report any suspected cases of pulmonary arterial hypertension associated with the use of the medicine to the TGA.

Dasatinib (Sprycel) is an oral tyrosine kinase inhibitor approved for the treatment of Philadelphia chromosome positive (Ph+) chronic myeloid leukaemia (CML) and Ph+ acute lymphoblastic leukaemia (ALL).

Pulmonary arterial hypertension (PAH) is a rare subtype of pulmonary hypertension, characterised by smooth muscle cell hyperplasia and vascular remodelling of the pulmonary arteries. This results in elevated mean pulmonary arterial pressure (>25 mmHg at rest or >30 mmHg during physical activity) as measured by right heart catheterisation.[1]

Detection and reporting

In the five years from June 2006, 60 serious cases of pulmonary hypertension were reported worldwide in association with dasatinib use to the sponsor's global pharmacovigilance database. Of these 60 cases, 36 cases were reported as pulmonary hypertension, and 24 cases were reported as PAH, including a subset of 12 cases of PAH confirmed by right heart catheterisation. In these 12 cases, PAH was reported after initiation of therapy with dasatinib, including after more than one year of therapy. Patients diagnosed with PAH during dasatinib therapy were often taking concomitant medications and had comorbidities in addition to the underlying malignancy.

To date, the TGA has received one report of reversible PAH secondary to dasatinib treatment for CML.

PAH has an insidious onset and patients with early or mild disease may be asymptomatic. Dyspnoea and reduced exercise capacity are typical early symptoms, which may progress to angina, exertional near-syncope, and signs of right heart failure. Given the high degree of clinical suspicion necessary to make the diagnosis, many cases may be undiagnosed and go unreported.

PAH may be at least partially reversible following cessation of dasatinib. Improvements in haemodynamic and clinical parameters have been observed in patients with PAH following cessation of dasatinib therapy.

The potential for a class-effect involving other tyrosine kinase inhibitors has not yet been investigated. The related drugs, imatinib and nilotinib, have not been implicated in reports of PAH to date. Compared with these, dasatinib appears to have a broader range of activity, affecting multiple kinase and non-kinase targets.[2] This provides a possible explanation for dasatinib-associated PAH and the observed differences in toxicities of drugs within this therapeutic class.

Important information for prescribers

Before commencing dasatinib therapy, patients should be evaluated for signs and symptoms of underlying cardiopulmonary disease. Patients taking dasatinib who develop symptoms of PAH, such as dyspnoea and fatigue, should be evaluated for more common aetiologies, including pleural effusion, pulmonary oedema, anaemia or lung infiltration. Treatment should be withheld in these patients during evaluation. If no alternative diagnosis is found, the diagnosis of PAH should be considered. If PAH is confirmed, dasatinib should be permanently discontinued. Further information is available in the dasatinib Product Information.[3] Prescribers are encouraged to report any suspected cases to the TGA.

REFERENCES

1. MacLean MR, Herve P, Eddahibi S, Adnot S. 5-hydroxytryptamine and the pulmonary circulation: receptors, transporters and relevance to pulmonary arterial hypertension. Br J Pharmacol 2000;131:161-8.
2. Rasheed W, Flaim B, Seymour JF. Reversible severe pulmonary hypertension secondary to dasatinib in a patient with chronic myeloid leukaemia. Leuk Res 2009;33:861-4.
3. Sprycel Product Information. Bristol-Myers Squibb Australia Pty Ltd. 2011 Jul.

MEDICINES SAFETY UPDATE

Pulmonary oedema associated with topical phenylephrine

Health professionals are reminded of the potential for serious systemic adverse effects, including pulmonary oedema, when topical phenylephrine is used concomitantly with a beta blocker.

Evidence of risk

Phenylephrine, an alpha agonist, is used as a topical vasoconstrictor in ear, nose and throat surgery and as a pupil dilator in eye surgery. There are published case reports of patients who developed pulmonary oedema associated with topical phenylephrine used in the perioperative setting.[1] In the majority of cases, this occurred after a beta blocker was given in an attempt to correct hypertension likely due to systemic absorption of the topical phenylephrine.

Published guidelines

The New York State Department of Health developed guidelines following the intraoperative death of a four-year-old attributed to topical phenylephrine.[1]

These guidelines advise that:

- the lowest effective dose of topical phenylephrine should be given to minimise the potential for systemic adverse effects
- beta blockers and calcium channel blockers should not be used to treat alpha agonist-induced hypertension (as a result of systemic absorption)
- anaesthetists should be consulted prior to administration of phenylephrine (or any other medication) to the surgical site.

REFERENCE

1. Groudine SB, Hollinger I, Jones J, DeBouno BA. New York State Guidelines on the topical use of phenylephrine in the operating room. Anaesthesiology 2000;92:859-64.

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies.
We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website and with the August issue of *Australian Prescriber*
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

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For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

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