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Department of Health and Ageing
Therapeutic Goods Administration

Medicines Safety Update

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In this issue

Montelukast – neuropsychiatric risks

Health professionals are reminded of the possibility of neuropsychiatric adverse events, including suicidal ideation, in children, adolescents and adults treated with montelukast. Health professionals should be aware of these potential adverse effects and advise patients and parents to seek medical advice should they occur.

Montelukast is a leukotriene receptor antagonist approved for the prophylaxis and treatment of chronic asthma in adults and children aged 2 years and older, and for the symptomatic treatment of seasonal allergic rhinitis.

It is available on the Pharmaceutical Benefits Scheme (streamlined authority) as a 'first-line preventer medication, as the single preventer agent for children aged 2 to 5 years with frequent intermittent or mild persistent asthma, as an alternative to sodium cromoglycate or nedocromil sodium'.

The Product Information (PI) for montelukast contains a precaution describing the possibility of multiple neuropsychiatric adverse events, including suicidal ideation, depression, agitation, aggressive behaviour, hallucinations, insomnia, somnambulism and tremor, as well as others.

Reported cases

Suspected neuropsychiatric adverse events in adult, adolescent and paediatric patients taking montelukast have been reported to the TGA.

Between 1 January 2000 and 1 January 2013, the TGA received reports of neuropsychiatric adverse events in 58 children and adolescents being treated with montelukast. Among the adverse events were five reports of suicidal ideation, five reports of depression and eight reports of agitation. Other neuropsychiatric reactions reported included nightmares, altered mood and insomnia. In many cases, patients experienced multiple neuropsychiatric reactions.

Although the number of reports is small, the inherent difficulty in establishing psychiatric diagnoses in children could contribute to under-reporting of related effects to the TGA.

Information for health professionals

Health professionals are reminded of the potential for neuropsychiatric adverse effects during treatment with montelukast, particularly when initiating therapy and increasing the dose. This is especially important if the patient is a child.

Health professionals should consult the PI for further information on potential neuropsychiatric adverse events and carefully evaluate the risks and benefits of continuing treatment with montelukast if such events occur.

In the case of children, caregivers should also be made aware of these potential adverse effects and instructed to seek medical advice if they have any concerns.

Health professionals are encouraged to report any suspected adverse events to the TGA.

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

TGA Health Safety Regulation

MEDICINES SAFETY UPDATE

Use of 2013 seasonal influenza vaccines in children

The TGA advises health professionals that, for the 2013 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. Fluvax should not be used in children under 5 years and should only be used in children aged 5 to under 9 years based on careful consideration of potential benefits and risks in the individual child.

During the 2010 influenza season, an excess number of febrile reactions and febrile convulsions occurred in children under 5 years after immunisation with one of the registered seasonal influenza vaccines, Fluvax.[1] As a result, the approved indication for Fluvax was changed to 5 years and over, with special precautions in children aged 5 to under 9 years.

Vaccine changes

Following a review of the strains of influenza that were circulating in the Southern Hemisphere, the Australian Influenza Vaccine Committee recommended changes to two of the strains in the 2013 vaccine compared with the 2012 vaccine. Details of the strains were announced on the TGA website.

The influenza strains in the 2013 vaccines are the same as the strains in the influenza vaccines used in the recent Northern Hemisphere winter. The TGA is reviewing surveillance data from the Northern Hemisphere to ensure there have been no unexpected adverse events related to these strains and, with the States and Territories, will be closely monitoring adverse event reports once the vaccination program commences.

Recommendations for use

For the 2013 influenza season, the TGA has registered five vaccines for use in children, with the indications shown in the table. An additional vaccine, Intanza (Sanofi Pasteur), is only registered for use in adults aged 18 to 59 years.

Adverse events following 2012 influenza vaccination

There were 435 adverse events reported to the TGA following vaccination with 2012 influenza vaccines, including 66 cases that were classified as serious.

Of these, 28 reports were of adverse events in children aged under 5 years and 9 reports were of adverse events in children aged 5 to under 9 years.

The TGA is aware that there were cases of inadvertent administration of Fluvax to children aged under 5 years, including four cases that resulted in adverse event reports. To minimise the risk of inadvertent administration in 2013, Fluvax's sponsor, bioCSL, has worked with the TGA to implement clearer warnings on the label and packaging, as well as in the black box warning in the Product Information (PI).

For further information about individual vaccines, please refer to the relevant PI document.

Reporting of adverse events following influenza vaccination

Please 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.

Table
2013 seasonal influenza vaccines approved for use in children

Vaccine	Sponsor	Approved indication
Agrippal	Novartis Vaccines and Diagnostics	6 months and over
Fluarix	GlaxoSmithKline	6 months and over
Influvac*	Abbott Australasia	6 months and over
Vaxigrip*	Sanofi Pasteur	6 months and over
Fluvax**	bioCSL	5 years and over

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

** Febrile events have been observed in children aged 5 to under 9 years after immunisation with Fluvax. Therefore, in this age group, a decision to vaccinate with the 2013 Southern Hemisphere formulation of Fluvax vaccine should be based on careful consideration of potential benefits and risks in the individual.

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

Denosumab and severe hypocalcaemia

Health professionals are reminded to closely monitor patients being treated with denosumab for signs of severe hypocalcaemia, which in some cases can be fatal. Pre-existing hypocalcaemia must be corrected before initiating therapy with denosumab.

Denosumab is available in Australia as two brands, Prolia and Xgeva, which have different indications.

Prolia (60 mg) is given once every 6 months for the treatment of osteoporosis in postmenopausal women, and for the treatment of men with osteopenia who are receiving androgen deprivation therapy for non-metastatic prostate cancer.

Xgeva (120 mg) is given once every 4 weeks for the prevention of skeletal-related events in adults with bone metastases from solid tumours.

Denosumab is a fully human monoclonal antibody to the receptor activator of nuclear factor-κB ligand (RANKL) that blocks its binding to receptor activator of nuclear factor-κB (RANK), inhibiting the development and activity of osteoclasts, decreasing bone resorption, and increasing bone density.[1]

Hypocalcaemia is a known risk with denosumab, especially in patients who:

- are predisposed to hypocalcaemia (for example, those with a history of hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes and excision of small intestine)
- have severe renal impairment (creatinine clearance < 30 mL/min)
- are receiving dialysis.

Signs and symptoms of hypocalcaemia include altered mental status, tetany, seizures and QTc prolongation.

Hypocalcaemia as a result of denosumab most commonly occurs in the first 6 months of treatment, but can occur at any time. The risk of severe hypocalcaemia is greater with use of Xgeva, although cases have also been reported in patients using Prolia.

Detection and reporting

Last year, a review of international postmarket data by the sponsor, Amgen, found that severe symptomatic hypocalcaemia occurred at an estimated rate of 1–2% in patients treated with Xgeva.[2] Some of these cases were found to be fatal. Amgen wrote to health professionals in September 2012, advising them of this information.

From 1 January 2011 to 25 October 2012, the TGA had received eight reports of hypocalcaemia in patients being treated with Xgeva. In all but one case, Xgeva was the sole suspect. During the same period, the TGA received 10 reports of hypocalcaemia with Prolia. In eight of those cases, Prolia was the sole suspect.

Changes to the Product Information

The precaution in the Xgeva Product Information (PI) regarding hypocalcaemia has been updated to advise health professionals that severe symptomatic hypocalcaemia has been reported in the postmarketing setting. Similar text has also been added to the adverse effects section.

The adverse effects section of the Prolia PI has been updated to advise health professionals that rare events of severe symptomatic hypocalcaemia have been reported in patients at increased risk of hypocalcaemia. The PI was also updated to specify that atypical femoral fractures have been reported in patients being treated with Prolia.

Advice for health professionals

Pre-existing hypocalcaemia must be corrected before initiating therapy with denosumab.

It is recommended that health professionals monitor the calcium levels of patients being treated with Prolia, especially if they are predisposed to hypocalcaemia. To reduce the risk of hypocalcaemia, patients must be adequately supplemented with calcium and vitamin D.

Supplementation with calcium and vitamin D is required for all patients receiving Xgeva (unless hypercalcaemia is present).

For full prescribing details, refer to the Xgeva and Prolia PIs, available on the TGA website.

Patients being treated with denosumab should be informed about the signs and symptoms of hypocalcaemia (for example, altered mental status, tetany and seizures) and of the need to seek immediate medical attention if they experience any of them.

REFERENCES

1. Cummings SR et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; 361:756-65.
2. Health Canada. Xgeva (denosumab) – risk of severe symptomatic hypocalcemia, including fatal cases – for health professionals. 2012.

MEDICINES SAFETY UPDATE

Thank you for reporting

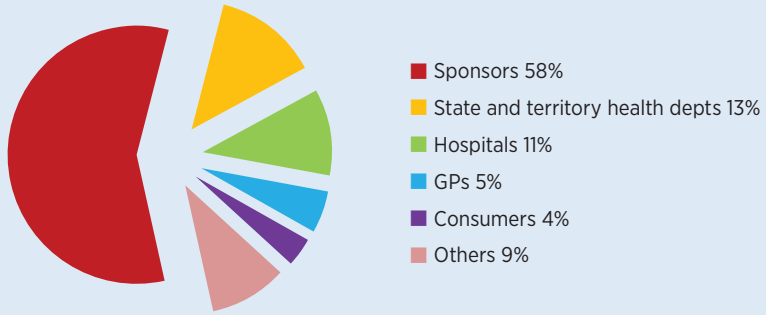
The TGA received approximately 14 500 adverse event reports during 2012. This was a similar number to those received during the previous year.

In recent years, sponsors have become the predominant reporter of adverse events. In 2012, sponsors were responsible for approximately 8350 reports (58% of all reports received) – demonstrating their commitment to meeting pharmacovigilance requirements, which support the TGA's mission to ensure ongoing medicine, vaccine and medical device safety in Australia.

Meanwhile, general practitioners (GPs) and consumers made a comparatively small number of reports in 2012. GPs contributed 5% of reports received last year, which was a decrease on the 7% they contributed in 2011.

The TGA aims to stimulate greater reporting from GPs and consumers in the future, with greater promotion of reporting avenues (such as the 'blue card') and other initiatives under the TGA's blueprint reforms that will support easier reporting. As part of the TGA's aim to increase transparency, it is working towards making information about medicines and medical devices that are being monitored publicly available. Further information about these activities will be provided as they develop.

Figure
Sources of adverse event reports made to the TGA in 2012



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, and 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 October 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.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

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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