Australian Government
Department of Health
Therapeutic Goods Administration

Medicines Safety Update

Volume 7, Number 4, August 2016

In this issue

Bcr-Abl tyrosine kinase inhibitors and hepatitis B virus reactivation

Health professionals are advised that cases of hepatitis B virus reactivation have occurred in patients who are chronic carriers of the virus after they received Bcr-Abl tyrosine kinase inhibitors. Some cases resulted in acute hepatic failure or fulminant hepatitis leading to liver transplantation or a fatal outcome.

Bcr-Abl tyrosine kinase inhibitors (TKIs) are indicated for the treatment of specific blood cancers including Philadelphia chromosome positive chronic myeloid leukaemia (CML). Bcr-Abl TKIs that are marketed in Australia include imatinib, nilotinib, dasatinib and ponatinib, which each have different indications.

Review of data

The TGA has recently evaluated a cumulative review of data from clinical trials and post-marketing experience by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), which showed hepatitis B virus (HBV) reactivation after use of Bcr-Abl TKIs in chronic HBV carriers. The EMA's case reports indicated that HBV reactivation could occur at any time during Bcr-Abl TKI treatment. Some patients had a documented history of HBV, while in other cases the serologic status at baseline was not known. An increase in viral load or positive serology was observed in patients when diagnosed with HBV reactivation.

Consequently, the PRAC recommended that sponsors of Bcr-Abl TKIs update their European product label.[1,2]

Based on its review, the TGA considers HBV reactivation a class-effect of Bcr-Abl TKIs, although the mechanism and the frequency of HBV reactivation during exposure are not known at this time.

The TGA has worked with sponsors of Bcr-Abl TKIs in Australia to include precautionary statements about HBV reactivation appropriate to each product in their Product Information (PI) documents.

Information for health professionals

Health professionals are advised to review the relevant PI for further information about:

- HBV testing before initiating treatment with a Bcr-Abl TKI
- consultation with experts in liver disease and/or HBV in patients with positive HBV serology and for patients who test positive for HBV infection during treatment.

Patients who are carriers of HBV who require treatment with Bcr-Abl TKIs should be closely monitored for signs and symptoms of active HBV infection throughout their treatment and for several months after stopping treatment.

REFERENCES

1. EMA Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the meeting on 07-10 September 2015. 4.1.7. Tyrosine kinase inhibitors (TKI): bosutinib – BOSULIF (CAP); dasatinib - SPRYCEL (CAP); imatinib – GLIVEC (CAP); nilotinib – TASIGNA (CAP); ponatinib – ICLUSIG (CAP). 8 October 2015
2. EMA Pharmacovigilance Risk Assessment Committee (PRAC) Recommendations on signals. Adopted at the PRAC meeting of 8-11 February 2016. 1.1. Bcr-abl tyrosine kinase inhibitors: imatinib; dasatinib; nilotinib; bosutinib; ponatinib – Hepatitis B virus (HBV) reactivation.

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

TGA Health Safety Regulation

Denosumab and QT prolongation

Product Information documents for denosumab products have been updated regarding the potential risk of QT interval prolongation associated with hypocalcaemia. This issue was identified during a TGA assessment of adverse event reports relating to this medicine.

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

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

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

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

Product Information update

Hypocalcaemia is a known effect of denosumab and was already captured in the Product Information (PI). However, there was previously no reference to QT prolongation, which is a potentially life-threatening disorder, or to severe symptomatic hypocalcaemia.

The following sections of the PI have been updated:

- Precautions
  - in the post-marketing setting, severe symptomatic hypocalcaemia has been reported, with most cases occurring in the first weeks of initiating therapy (although it can occur later)
  - routine clinical monitoring of calcium levels is recommended
  - information about the symptoms of hypocalcaemia and the importance of maintaining calcium levels should be given to all patients being treated with denosumab.
- Adverse Effects
  - examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status
  - symptoms of hypocalcaemia in denosumab clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.

This updated information has harmonised the Australian PIs with the European Union Summary of Product Characteristics for these products.

Isotretinoin and psychiatric adverse event

Following a TGA evaluation of the findings of a UK Medicines and Healthcare Products Regulatory Agency report regarding isotretinoin and psychiatric adverse reactions, health professionals are reminded of the potential risk of psychiatric adverse risks and the need for careful psychological assessment before and during isotretinoin treatment.

Isotretinoin, which is marketed in Australia as Roaccutane and under multiple generic brand names, is a retinoid that inhibits sebaceous gland function and keratinisation.

It is indicated for the treatment of severe cystic acne. However, because of significant adverse events associated with its use, isotretinoin should be reserved for patients with severe cystic acne who are unresponsive to conventional therapy, including systemic antibiotics.

The Medicines and Healthcare Products Regulatory Agency (MHRA) public assessment report concluded that it was important to recognise that acne was associated with psychiatric disorders, regardless of whether or not isotretinoin was used. Available data were insufficient to establish a causal association, but also could not rule out a link between this medicine and psychiatric disorders.[1]

The MHRA found that current warnings in the UK product labelling were appropriate and no further

regulatory action was required. However, patients should be regularly screened and monitored for psychiatric disorders and education of patients, as well as their family and friends, could possibly be improved.

The TGA found similarly that psychiatric adverse reactions, including depression and suicidality, are a known risk associated with the use of isotretinoin and are adequately communicated in the Australian Product Information and Consumer Medicine Information (CMI).

However, the TGA's assessment recommended that health professionals be reminded that clinically significant depression can occur in patients taking this medicine and care should be taken in patients with a history of psychiatric disorders.

All patients should be screened and monitored for signs of depression and referred for appropriate treatment if necessary.

It is advised that health professionals urge patients being treated with isotretinoin to read the CMI and, in particular, to take note of the information regarding potential psychiatric disorders and the need for them to contact their doctor or pharmacist if they experience associated symptoms. It may also be appropriate to discuss these issues with the patient's family members.

REFERENCE

1. Medicines and Healthcare Products Regulatory Agency. Review of isotretinoin and psychiatric adverse reactions. November 2014

Medicine shortages information

The Medicine Shortages Information Initiative provides information about a temporary or permanent disruption to the supply of a prescription medicine. Health professionals and consumers are invited to subscribe to the Medicine Shortages email list to receive an alert when there is new or updated medicine shortage information reported to the TGA.

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
- **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 Pharmacovigilance and Special Access Branch on 1800 044 114.

DISCLAIMER

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 Pharmacovigilance and Special Access Branch at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Pharmacovigilance and Special Access Branch

Editor:
Dr Jane Cook

Deputy Editor:
Mr Michael Pittman

Acting TGA Principal Medical Adviser:
Dr Tony Gill

Contributors include:
Ms My Di Luu
Dr Bronwen Harvey
Dr Iga Policinska
Mr Saqif Shams