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Medicines Safety Update

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Ibrutinib – ventricular tachyarrhythmia, hepatitis B reactivation and infection

Health professionals are advised that the Product Information for ibrutinib is being updated with new safety information relating to reports of ventricular tachyarrhythmia, and risk of hepatitis B reactivation and opportunistic infection.

Ibrutinib, which is marketed in Australia as Imbruvica, is a selective and covalent inhibitor of Bruton's tyrosine kinase. It is used for the treatment of certain types of blood cancers, including mantle cell lymphoma and Waldenstrom's macroglobulinaemia chronic lymphocytic leukaemia (including small lymphocytic lymphoma).

Updates to the Precautions and Post Marketing Data sections of the Product Information (PI) are being made following TGA evaluation of new data on the safety of ibrutinib.

Ibrutinib continues to have a favourable risk-benefit profile for treating patients with indications specified in the Australian PI.

Ventricular tachyarrhythmia

Cases of ventricular tachyarrhythmia have been reported with the use of ibrutinib.

In a 2017 study of relevant case reports from post-marketing sources and clinical trial data, 11 cases of ventricular tachycardia/ventricular fibrillation and six additional cases of sudden cardiac death in patients exposed to ibrutinib were identified. In 12 of these 17 cases, the events occurred without any evidence of prior cardiac history.[1]

There were 52 cases of ventricular tachyarrhythmia reported in post-marketing settings.

Based on current evidence, the role of ibrutinib in causing ventricular arrhythmia, cardiac arrest and sudden cardiac death is currently unknown.

However, due to the potential severity of these events, ibrutinib should be temporarily discontinued in patients who develop signs and/or symptoms of ventricular tachyarrhythmia, including palpitations, chest pain, dyspnea, dizziness or fainting.

A thorough assessment of risk-benefit should be made before making any decision to restart therapy.

Hepatitis B reactivation

A cumulative review of data from clinical trials and post-marketing cases identified eight reports of hepatitis B reactivation in ibrutinib-treated patients where the role of ibrutinib was considered probable or possible.

The time-to-onset was variable. Ibrutinib was discontinued or interrupted and patients were managed with hepatitis B antiviral medication according to their local standard of care. Reduction of hepatitis B viral load was achieved in the majority of cases. In several cases, the role of ibrutinib therapy in the onset of the event was confounded by prior or concomitant chemoimmunotherapy regimens associated with viral reactivation. Some of the patients had a documented history of hepatitis B, and in other cases, baseline hepatitis B serology status was not reported. To date, there have been no reports of fulminant liver failure leading to liver transplantation. One fatal outcome has been reported in a patient due to hepatitis B reactivation and concurrent metastatic melanoma involving liver, lung and spleen. In company-sponsored clinical trials, patients with active hepatitis B were excluded.

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TGA Health Safety Regulation

The role of ibrutinib in reactivation of hepatitis B virus is not currently known. However, given the existence of several reported cases, the PI is being updated to reflect the updated safety information.

Hepatitis B virus status should be established before initiating treatment with ibrutinib.

If your patient has positive hepatitis B serology indicative of prior infection, consult a liver disease expert before commencing treatment with ibrutinib.

Patients with positive hepatitis B serology who are being treated with ibrutinib must be regularly monitored to detect hepatitis B reactivation early.

Opportunistic infection

Infections (including sepsis, neutropenic sepsis, bacterial, viral or fungal infections) have been observed in patients treated with ibrutinib. Some of these infections resulted in hospitalisation and, in some cases, death.

A cumulative review of clinical trial and post marketing cases of aspergillosis in ibrutinib-treated patients reported a higher than expected number of confirmed invasive cases in one investigator-initiated study, which used an unapproved combination treatment regimen for an unapproved indication in Europe. The review identified 157 cases of aspergillosis in patients treated with ibrutinib in the post marketing setting, 43 of which were fatal.

A cumulative review of pneumocystis infections in clinical trial and post marketing reports in ibrutinib-treated patients was also undertaken. The review identified 44 cases of Pneumocystis Jirovecii pneumonia (PJP), of which none were fatal. The crude incidence of PJP infection from the ibrutinib clinical trials between the ibrutinib treatment arm and the comparator arm was 0.53% compared with 0.40% respectively.

In many cases reported in the post marketing setting, patients who experienced opportunistic infections had other baseline or concurrent factors which may increase the risk of developing these infections including steroid use, hypogammaglobulinemia and immunosuppression. The role of ibrutinib in these opportunistic infections continues to be monitored.

Given the relatively high number of fatal cases with opportunistic infection, healthcare professionals should consider prophylaxis according to standard of care for patients who are at an increased risk of opportunistic infection.

REFERENCE

1. Lampson BL, et al. Ventricular arrhythmias and sudden death in patients taking ibrutinib. Blood 2017 129: 2581–84.

Improving Product Information

A new format for Product Information has been developed to make clinical information easier to find and to align with other international regulators.

Product Information (PI) documents provide health professionals with a summary of the scientific information relevant to the safe and effective use of a particular medicine. However, feedback from health professionals and stakeholder organisations suggests that the current PI format can make the most useful information harder to find than it should be.

The current PI format requires information on a medicine's pharmacology and clinical trials data to be presented ahead of information relating to the clinical use of the medicine.

The critical information for health professionals includes the indications, dosage and administration instructions, contraindications, precautions and adverse events information.

In the current format, much of this information is located in the middle or towards the end of the PI, which can frequently be 20 or more pages long.

The TGA has developed a new format in consultation with health professionals, and relevant professional bodies have expressed their support for the changes. In addition, the new format has been developed to align with the formatting requirements of other international regulators, specifically the New Zealand medicines regulator Medsafe and the European Medicines Agency.

New PI format

The key changes are:

- the content of the PI is being re-ordered to bring critical clinical information together at the front of the document
- the headings and subheadings have been updated to align with headings used internationally.

The new PI format will be introduced for new medicines approved after 1 January 2018. Existing PI documents will be updated to the new format during a three-year transition period.

Codeine-containing products – use in children and ultra-rapid metabolisers

Health professionals are advised that the recommendations of a TGA safety review of codeine use in children and rapid metabolisers have now been implemented.

The Product Information (PI) documents for all prescription codeine products have been updated to reflect the findings of the TGA's safety review.

Specifically, codeine products should no longer be used in children under 12 years of age, or in children aged 12-18 years who have recently undergone surgery to remove their tonsils or adenoids.

Codeine should also not be used by breastfeeding mothers or in patients known to be ultra-rapid metabolisers.

Most PIs for over-the-counter codeine products now have warnings to not use these products in children aged under 12 years.

From 1 February 2018, all Schedule 2 (Pharmacy Medicine) and Schedule 3 (Pharmacist Only Medicine) codeine-containing products will be rescheduled to Schedule 4 (Prescription Only Medicine).

In the meantime, the TGA has identified a small number of over-the-counter codeine products, all of which are tablets, that are currently being marketed and still have dosage instructions for children aged 6-12 years.

The sponsors of these products have written to pharmacists to inform them of the relevant safety information including that these products should not be used in children under 12 years of age.

Please be mindful of these changes, especially during the transition period for the rescheduling of these products, and advise patients accordingly.

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.

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