HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

Imbruvica (ibrutinib) – New risk minimisation measures, including dose modification recommendations, due to increased risk of serious cardiac events

Imbruvica is authorised in Ireland and across the EU as a single agent or in combination with other therapeutics for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), chronic lymphocytic leukaemia (CLL), or Waldenström's macroglobulinaemia (WM). *

Based on an assessment of available data on the cardiotoxicity of ibrutinib, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended further measures to minimise risks and updates to product information**.

The assessment of data from a randomised controlled trial pool of ibrutinib showed an almost 5-fold higher crude incident of sudden cardiac death, sudden death, and cardiac death in the ibrutinib arm (11 cases; 0.48%) versus the comparator arm (2 cases; 0.10%). When adjusted for exposure, a 2-fold increase in the incidence rate (EAIR, expressed as number of subjects with events divided with patient-months at risk) of events of sudden cardiac death, sudden death or cardiac death was observed in the ibrutinib arm (0.0002) versus the comparator arm (0.0001) (see Direct Healthcare Professional Communication (DHPC) for further details)§.

Based on the available data, the PRAC consider that patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of events including sudden fatal cardiac events.

Further Measures to Minimise Risk of Serious Cardiac Events

- Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating ibrutinib.
- Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed. Consider further evaluation (e.g., ECG, echocardiogram), as indicated for patients in whom there are cardiovascular concerns.
- For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment with ibrutinib; alternative treatments may be considered.
- Product information has been updated to include a warning in section 4.4 of the SmPC and cardiac arrest has been added as an adverse drug reaction with a frequency of uncommon in section 4.8 of the SmPC.
- Product information has also been updated with advice on dose modification for patients experiencing cardiac events.
- Healthcare professionals can reference the product information of Imbruvica for full details of the revised measures as well as all current warnings and precautions for use.

Key Message

- Fatal and serious cardiac arrhythmias and cardiac failure have been reported in patients treated with ibrutinib.
- Patients with advanced age, Eastern Cooperative Oncology Group (ECOG) performance status ≥2, or cardiac co-morbidities may be at greater risk of events including sudden fatal cardiac events.
- Appropriate clinical evaluation of cardiac history and function should be performed prior to initiating treatment.
- Patients should be carefully monitored during treatment for signs of clinical deterioration of cardiac function and clinically managed.
- For patients with relevant risk factors for cardiac events, carefully assess benefit/risk before initiating treatment; alternative treatment may be considered.
- Product information has been updated with new recommendations regarding dose modification in case of cardiac failure and cardiac arrhythmias.
- Further details on measures to minimise risk of serious cardiac events are available in a recent DHPC and the product information of Imbruvica

** Imbruvia is indicated as a single agent for the treatment of adult patients with relapsed or refractory MCL; as a single agent or in combination with rituximab or obinutuzumab or venetoclax for the treatment of adult patients with previously untreated CLL; as a single agent or in combination with bendamustine and rituximab for the treatment of adult patients with CLL who have received at least one prior therapy; as a single agent for the treatment of adult patients with WM who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemo-immunotherapy. Ibrutinib in combination with rituximab is also indicated for the treatment of adult patients with WM.*

Further details are available from product information at http://www.hpra.ie and http://www.ema.europa.eu.

*** The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie or www.ema.europa.eu.*

§ *https://www.hpra.ie/docs/default-source/default-document-library/important-safety-information-imbruvica-(ibrutinib).pdf?sfvrsn=0*