SFDA SAFETY SIGNAL

"A signal is defined by the SFDA as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature"

2-8-2020

Saudi Food and Drug Authority (SFDA) – Safety Signal of Ibrutinib and the Potential Risk of Cardiac Failure

*The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of **Cardiac Failure** associated with the use of **Ibrutinib**. The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction Ibrutinib is a selective, potent, and irreversible small-molecule inhibitor of Bruton's tyrosine kinase (Btk). It forms a covalent bond with a cysteine residue (CYS-481) at the active site of Btk, leading to inhibition of Btk enzymatic activity [1]. The drug is indicated to treat certain type of cancers such as mantle cell lymphoma (MCL), chronic lymphocytic leukaemia and Waldenström's macroglobulinaemia (WM) [2]. Cardiac failure is a condition referred to inability of heart muscle to pump adequate blood to human body organs. There are multiple types of cardiac failure including left and right-sided heart failure, systolic and diastolic heart failures [3]. The aim of this review is to evaluate the risk of cardiac failure associated with the use of ibrutinib and to suggest regulatory recommendations if required.

Methodology Signal Detection team at the National Pharmacovigilance Center (NPC) of Saudi Food and Drug Authority (SFDA) performed a comprehensive signal review using its national database as well as the World Health Organization (WHO) database (VigiBase), to retrieve related information for assessing the causality between cardiac failure and ibrutinib [4]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [5]

Results

Case Review: The number of resulted cases for the combined drug/adverse drug reaction are 212 global ICSRs as of July 2020 [4]. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.9 and above (35 ICSRs); the value 1.0 indicated the highest score for best-written ICSRs. Among the reviewed cases, more than half of them provides supportive association (4 probable and 15 possible cases).

Data Mining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by

WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association, considering the null value equal to zero. The results of (IC=1.5) revealed a positive statistical association for the drug/ADR combination, which means "Ibrutinib" with "Cardiac Failure" have been observed more than expected when compared to other medications available in WHO database [4].

Conclusion

The weighted cumulative evidences identified from causality assessment of the reported cases and data mining are sufficient to support a causal association between ibrutinib and cardiac failure. Health regulators and health care professionals must be aware for the potential risk of cardiac failure associated with ibrutinib and the monitoring of any signs or symptoms in treated patients is essential.

Report Adverse Drug Events (ADRs) to the SFDA

The SFDA urges both healthcare professionals and patients to continue reporting adverse drug reactions (ADRs) resulted from using any medications to the SFDA either online, by regular mail or by fax, using the following contact information:

National Pharmacovigilance Center (NPC)
Saudi Food and Drug Authority-Drug sector
4904 northern ring branch rd
Hittin District
Riyadh 13513 – 7148
Kingdom of Saudi Arabia
Toll free number: 19999
Email: NPC.Drug@sfda.gov.sa

References:

1. Parmar, S., Patel, K., & Pinilla-Ibarz, J. (2014). Ibrutinib (imbruvica): a novel targeted therapy for chronic lymphocytic leukemia. *Pharmacy and Therapeutics*, *39(7)*, 483.
2. Electronic medicines compendium (2020), Imbruvica Summary of product Caractaristics (SPC); Available at: https://www.medicines.org.uk/emc/product/10025/smpc [Accessed 15/7/2020].
3. Mayo Clinic (2020), Heart Failure. Available at https://www.mayoclinic.org/diseases-conditions/heart-failure/symptoms-causes/syc-20373142 [Accessed 15/7/2020].
4. Uppsala Monitoring Center (UMC) (2020), Vigilyze database; Available at: https://vigilyze.who-umc.org [Accessed 15/7/2020].
5. Uppsala Monitoring Center (UMC) (2020), The use of the WHO-UMC system for standardized case causality assessment; Available at https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf?ua=1 [Accessed 23/7/2020].