

## 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”*

05-08-2024

### Saudi Food and Drug Authority (SFDA) – Safety Signal of Verapamil and the Risk of Hepatitis cholestatic

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

#### Introduction

Verapamil is a first-generation calcium channel blocker used for treatment of hypertension, angina pectoris and supraventricular tachyarrhythmias. <sup>[1]</sup> Cholestasis is a pathological condition in which various intrahepatic or extrahepatic factors impede bile formation, secretion, or excretion, leading to increased flow of bile into the duodenum and blood. <sup>[2]</sup> The aim of this review is to evaluate the risk of Hepatitis cholestatic associated with the use of Verapamil and to suggest regulatory recommendations if required.

#### Methodology

Signal Detection team at SFDA performed a signal review using National Pharmacovigilance Center (NPC) database, and World Health Organization (WHO) database, VigiBase, with literature screening to retrieve all related information to assess the causality between Hepatitis cholestatic and Verapamil use. The search conducted on May 2024.

#### Results

**Case Review:** Signal detection team at SFDA have searched Saudi national database and WHO database to find individual case safety reports (ICSRs). The WHO database resulted in 60 global case-reports while no local cases found. The authors used signal detection tool (Vigilyze) to retrieve all reported global cases. <sup>[3]</sup> Authors also applied WHO-UMC causality assessment criteria on ICSRs with completeness score 0.8 and above (n=11). <sup>[4]</sup> Among them, 7 cases of Hepatitis cholestatic were probably or possibly linked to Verapamil while one case was unable to assess due to lack of essential information and the remaining 3 cases assessed as unlikely.

**Datamining:** 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. The IC result is (2.7) for this drug/ADR combination which reflects strong positive statistical association. <sup>[4]</sup>

**Literature:** The signal team searched the literature to find related publications linking this ADR to the drug. The search showed one published case-report of Hepatitis cholestatic following the use of Verapamil <sup>[5]</sup>

### **Conclusion**

The weighted cumulative evidence identified from assessed cases, disproportionality analysis, and literature are suggestive for causal association between Verapamil and Hepatitis cholestatic. Health care professionals and health regulators must be aware of the potential risk in drug recipients.

### **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@sfd.gov.sa](mailto:NPC.Drug@sfd.gov.sa)

### **References:**

- 1- LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Verapamil. [Updated 2017 Jan 11]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK548362/>
- 2- Lu, L., & Chinese Society of Hepatology and Chinese Medical Association (2022). Guidelines for the Management of Cholestatic Liver Diseases (2021). Journal of clinical and translational hepatology, 10(4), 757–769. <https://doi.org/10.14218/JCTH.2022.00147> [Accessed: 14/05/2024].
- 3- Vigilyze.who-umc.org. 2024. [online] Available at: <https://vigilyze.who-umc.org/> [Accessed: 14/05/2024].
- 4- World Health Organization WHO (2013). WHO-UMC system for standardised case causality assessment. Available at <https://www.who.int/publications/m/item/WHO-causality-assessment> [Accessed: 14/01/2024].
- 5- Kumar, K. L., & Colley, C. A. (1994). Verapamil-induced hepatotoxicity. The Western journal of medicine, 160(5), 485–486.