# 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"*

**25-09-2022**

## Saudi Food and Drug Authority (SFDA) – Safety Signal of Duloxetine and the Risk of Hepatic Necrosis

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

### Introduction

Duloxetine hydrochloride is a selective serotonin and norepinephrine reuptake inhibitor, although the exact mechanism of the antidepressant, central pain inhibitory, and anxiolytic actions in humans are unknown, it is believed to exert its antidepressant and pain inhibitory actions by potentiating the serotonergic and noradrenergic activity in the CNS. It has no significant affinity for adrenergic, dopaminergic, cholinergic, opioid, glutamate or histaminergic receptors in vitro and does not inhibit monoamine oxidase.[1] Hepatic necrosis is defined as death of hepatocytes, which maybe single cell, multiple cells in piecemeal, focal, multifocal, submassive or massive. Submassive hepatic necrosis is defined as necrosis involving 26%-75% of the parenchymal volume, while massive necrosis involves more than 75%.[2] The aim of this review is to evaluate the risk of hepatic necrosis associated with the use of duloxetine 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 hepatic necrosis and duloxetine use. The search conducted on June 2022.

### Results

**Case Review:** Signal detection team at SFDA have searched Saudi national database and WHO database to find individual case safety reports (ICSRs) of hepatic necrosis associated with duloxetine. While the search resulted in zero reported local cases, the search in the WHO database resulted in 23 global case-reports. The authors used signal detection tool (Vigilyze) to retrieve all reported cases. [3] Authors also applied WHO-UMC causality assessment criteria on ICSRs with completeness score (0.4) and above (n=10). Among them, 2 cases of hepatic necrosis were possibly linked to duloxetine while

the other 8 cases lack of sufficient information for assessing the causality. Additionally, six cases reported positive dechallenge reactions with duloxetine.

**Literature:** In June 2022, the author searched for eligible publication using terms "Duloxetine" and "hepatic necrosis".

This signal was detected from a Cohort study entitled "Surveillance of Antidepressant Safety (SADS): Active Signal Detection of Serious Medical Events Following SSRI and SNRI Initiation Using Big Healthcare Data". Hepatic necrosis was one of the identified serious adverse events. [4]

The study, objective was to propose and test a near real-time epidemiological surveillance system using sequential, cumulative analyses focusing on the detection and preliminary risk quantification of potential safety signals following initiation of selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs). In the total study population, 969,667 new users were included and followed for 461,506 person-years. Potential safety signals were detected with incidence rates as low as 0.9 per 10,000 person-years. Having eight different exposure drugs and 51 medical events, 31 unique combinations of potential safety signals were identified with a positive association to the event of interest in the exposed group. [4]

Another article describing a case series of Hepatotoxicity following the use of Duloxetine is been published in 2010. The aim of the study is to describe the presenting features and outcomes of 7 well-characterized patients with suspected duloxetine hepatotoxicity. The study conclusion was duloxetine hepatotoxicity developed within 2 months of drug intake and led to clinically significant liver injury. A spectrum of laboratory, histological, and extra-hepatic features were noted at presentation. [5]

**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, considering the null value equal to zero. The results of (IC= 1.4) revealed a positive statistical association for the drug/ADR combination. [3]

**Conclusion**

The weighted cumulative evidence identified from assessed cases, literature and datamining are sufficient to suggest causal association between duloxetine and hepatic necrosis. 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@sfda.gov.sa

**References:**

1- IBM Micromedex products (2022). Retrieved April 2, 2022, from https://www.micromedexsolutions.com/

2- Ndekwe, P., Ghabril, M. S., Zang, Y., Mann, S. A., Cummings, O. W., & Lin, J. (2017). Substantial hepatic necrosis is prognostic in fulminant liver failure. *World Journal of Gastroenterology*, *23*(23), 4303.

3- Vigilyze.who-umc.org. 2022. [online] Available at: <https://vigilyze.who-umc.org/> [Accessed 03/24/2022].

4- Aakjær, M., De Bruin, M. L., Kulahci, M., & Andersen, M. (2021). Surveillance of Antidepressant Safety (SADS): Active signal detection of serious medical events following SSRI and SNRI initiation using Big Healthcare Data. Drug Safety, 44(11), 1215–1230. https://doi.org/10.1007/s40264-021-01110-x

5- Vuppalanchi, R., Hayashi, P. H., Chalasani, N., Fontana, R. J., Bonkovsky, H., Saxena, R., ... & Drug-Induced Liver Injury Network (DILIN). (2010). Duloxetine hepatotoxicity: a case-series from the drug-induced liver injury network. Alimentary pharmacology & therapeutics, 32(9), 1174-1183.