

## 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”*

21-2-2021

### Saudi Food and Drug Authority (SFDA) – Safety Signal of Clopidogrel and the Risk of Hypertension

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

**Introduction** Clopidogrel is a prodrug that inhibits platelet aggregation. Clopidogrel must be metabolised by CYP450 enzymes to produce the active metabolite that inhibits platelet aggregation <sup>[1]</sup>. Clopidogrel is indicated for use in adult patients suffering from myocardial infarction (from a few days until less than 35 days), ischaemic stroke (from 7 days until less than 6 months) or established peripheral arterial disease <sup>[2]</sup>. Hypertension or high blood pressure is a common condition in which the long-term force of the blood against artery walls is high enough that it may eventually cause health problems, such as heart disease <sup>[3]</sup>. The aim of this review is to evaluate the risk of Hypertension associated with the use of Clopidogrel 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 Clopidogrel and the Risk of Hypertension <sup>[4]</sup> We used the WHO-Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases <sup>[5]</sup>

### Results

**Case Review:** The number of resulted cases for the combined drug/adverse drug reaction are 357 global ICSRs as of September 2020 <sup>[4]</sup>. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.8 and above (28 ICSRs); the value 1.0 indicated the highest score for best-written ICSRs. Among the reviewed cases, about half of them provides supportive association (1 certain, 4 probable, and 9 possible cases) and 5 positive dechallenges. In addition, a Saudi local case-report found with probable association and positive dechallenge.

**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= -0.6) revealed a negative statistical association for the drug/ADR combination, which means “Hypertension” with the use of “Clopidogrel” have been observed slightly less 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 are sufficient to support a causal association between Clopidogrel and the risk of Hypertension. Health regulators and health care professionals must be aware for this potential risk and shall monitor any signs or symptoms in treated patients.

### **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. Accord (2019), European Summary of Product Characteristics (SPC) of clopidogrel hydrogen sulfate (Clopidogrel) ®; Available at: <https://www.medicines.org.uk/emc/product/5288/smpe> Last updated on 11 Nov 2019 [Accessed 11/26/2019].
2. Sanofi, Saudi Summary of Product Characteristics (SPC) of clopidogrel (Plavix) ®; (retrieved from EURS).
3. Mayo clinic. (2020). High blood pressure (hypertension). Retrieved from: <https://www.mayoclinic.org/diseases-conditions/high-blood-pressure/symptoms-causes/syc-20373410> [Accessed 9/2/2020].
4. Uppsala Monitoring Center (UMC) (2020), Vigilyze database; Available at: <https://vigilyze.who-umc.org/> [Accessed 9/21/2020]
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](https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf?ua=1) [Accessed 23/7/2020].