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"

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Saudi Food and Drug Authority (SFDA) – Safety Signal of Erenumab and the Risk of Raynaud's Phenomenon

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

Introduction

Erenumab is a fully human IgG2 monoclonal antibody produced using recombinant DNA technology in Chinese hamster ovary (CHO) cells used for migraine prophylaxis. It binds to the calcitonin gene-related peptide (CGRP) receptor. CGRP is a neuropeptide that modulates nociceptive signaling and a vasodilator that has been associated with migraine pathophysiology [1]. Raynaud's Phenomenon is vasospastic disorder recognized by transitory, episodic, and reversible vasospasm of peripheral blood vessels and characterized by color changes ranging from white caused by constriction of digital arteries (ischemic phase) to bluish-cyanotic (cyanotic phase) and ultimately to red due to vasodilation (hyperemic phase) [2]. The aim of this review is to evaluate the risk of Raynaud's Phenomenon associated with the use of Erenumab 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 Erenumab and the risk of Raynaud's Phenomenon [3]. We used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [4].

Results

Case Review: There were 58 individual case safety reports (ICSRs) for the combined drug/adverse drug reaction as of May 2022 [3]. One case revealed probable association and 7 cases revealed a

possible association using the WHO causality assessment tool on 13 cases with completeness score (0.6) and above. Moreover, a positive dechallenge was reported in 2 cases [4].

Data Mining: Information component (IC), a tool developed by WHO-UMC to measure the reporting ratio, is used to estimate the disproportionality of the observed and expected reporting rates for drug/adverse drug reaction pairs. Positive IC values indicate a positive statistical association, whereas negative values indicate no statistical association. The results of (IC= 3.1) revealed that the drug/ADR combination has a positive statistical association. In other words, Raynaud's Phenomenon has been observed more than expected with Erenumab compared to other medications in the database [3].

Literature: the risk of Raynaud's Phenomenon in association with Erenumab was highlighted in literature:

A review included data from 4 double-blind, placebo-controlled studies of Erenumab in patients with chronic or episodic migraine was published in 2020. The pooled analysis aimed to examine if the rates of vascular (cardiovascular or cerebrovascular) adverse events were higher in the Erenumab group vs the placebo group of controlled clinical studies. Incidence of Raynaud's phenomenon following Erenumab exposure was <0.1% [5].

a 45-year-old woman who had migraine in her teens was started on Erenumab 70 mg, a monthly subcutaneous injection. The patient reported 40% improvement in headache severity and overall migraine symptoms. Two weeks after the second injection of Erenumab, she developed intermittent blue discoloration of both hands, which worsened over a period of 7–8 months on Erenumab treatment. The symptoms were worse in cold weather and improved in the summertime. As per the patent's, she had never experienced such symptoms before Erenumab administration. Symptoms improved by 70% with drug withdrawal [6].

Conclusion

The weighted cumulative evidence identified from the reported cases, data mining and literature are sufficient to support a causal association between Erenumab and the risk of Raynaud's Phenomenon. Health regulators and health care professionals must be aware of this potential risk and it is advisable to 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@sfda.gov.sa

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