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"

05-03-2024

Saudi Food and Drug Authority (SFDA) – Safety Signal of Testosterone and the Risk of Atrial Fibrillation

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

Introduction

Testosterone is indicated for replacement therapy in the male in conditions associated with symptoms of deficiency or absence of endogenous testosterone.During exogenous administration of androgens, endogenous testosterone release is inhibited through feedback inhibition of pituitary luteinizing hormone (LH). At large doses of exogenous androgens, spermatogenesis may also be suppressed through feedback inhibition of pituitary follicle stimulating hormone (FSH). [1] Atrial fibrillation, often called AFib or AF, is the most common type of treated heart arrhythmia. An arrhythmia is when the heart beats too slowly, too fast, or in an irregular way. When a person has AFib, the normal beating in the upper chambers of the heart (the two atria) is irregular, and blood doesn't flow as well as it should from the atria to the lower chambers of the heart (the two ventricles). AFib may happen in brief episodes, or it may be a permanent condition.[2] The aim of this review is to evaluate the risk of Atrial fibrillation associated with the use of Testosterone 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 Atrial fibrillation and Testosterone use. The search conducted on January 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 330 global case-reports while no local cases found. The authors used signal detection tool (Vigilyze) to retrieve all reported global cases. [3] Authors also applied WHO-UMC causality assessment criteria on ICSRs with completeness score 0.8 and above (n=19). [4] Among them, 3 cases of Atrial fibrillation were possibly

linked to Testosterone, 15 were not assessable due to lack of important information and finally only one case 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 (1.6) for this drug/ADR combination which reflects positive statistical association. [4]

Literature: The signal was detected from a study entitled (Cardiovascular Safety of Testosterone-Replacement Therapy. Atrial fibrillation mentioned in Investigator-Reported Adverse Events. [5]

Additional Evidence: The adverse reaction of interest is listed in adverse events section in Canadian Drug Monograph. [6]

Conclusion

The weighted cumulative evidence identified from assessed cases, disproportionality analysis, global regulatory and literature are sufficient to suggest causal association between Testosterone and Atrial fibrillation. 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- DailyMed - testosterone cypionate injection (no date) U.S. National Library of Medicine. Available at: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d7b57b68-dca6-4df2-b3f2-7017d7b69f17 [Accessed: 03/01/2024].

2- Atrial fibrillation (2022) Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/heartdisease/atrial_fibrillation.htm [Accessed: 03/01/2024].

3- Vigilyze.who-umc.org. 2024. [online] Available at: https://vigilyze.who-umc.org/ [Accessed: 03/01/2024].

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: 03/01/2024].

5- Lincoff, A.M. et al. (2023) 'Cardiovascular safety of testosterone-replacement therapy', New England Journal of Medicine, 389(2), pp. 107–117. doi:10.1056/nejmoa2215025.

6- Product information - health-products.canada.ca. Available at: https://pdf.hres.ca/dpd_pm/00046306.PDF [Accessed: 03/01/2024].