



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”

19-10-2026

Saudi Food and Drug Authority (SFDA) – Safety Signal of Leflunomide and the Risk of Rheumatoid lung

*The Saudi Food and Drug Authority (SFDA) recommends that all healthcare professionals be aware of the safety signal of **Rheumatoid lung** associated with the use of **Leflunomide**. The signal originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Leflunomide is a disease-modifying antirheumatic drug (DMARD) used to treat active rheumatoid arthritis and active psoriatic arthritis in adults. It works by reducing inflammation and slowing disease progression to improve physical function.^[1] Rheumatoid lung is a group of pulmonary complications associated with rheumatoid arthritis (RA), including interstitial lung disease, airway obstruction, pleural effusions, pulmonary hypertension, nodules, and fibrosis. It is often asymptomatic and can sometimes be the first sign of RA. Its exact cause is unknown, although certain RA medications have also been implicated as possible contributing factors.^[2] This review aims to evaluate this potential risk and to suggest regulatory recommendations if required.

Methodology

The Signal Detection Team at SFDA performed a signal review using the National Pharmacovigilance Center (NPC) database and the World Health Organization (WHO) database, Vigibase, along with a literature review to retrieve all relevant information and assess the potential link between rheumatoid lung and leflunomide use.

Results

Cases Review: The Signal Detection Team at SFDA searched the Saudi national database and the WHO database to identify individual case safety reports (ICSRs). The WHO database yielded 42 global case reports, while the NPC database yielded no local cases. The authors used the signal detection tool (VigiLyze) to retrieve global cases.^[3] The authors applied the WHO causality assessment tool to 30 cases with the highest completeness scores. Two cases were considered probably associated with leflunomide, six cases showed a possible association, two were assessed as unlikely to be associated, and the remaining 20 cases were unassessable.

Datamining: The disproportionality between the observed and expected reporting rates for a drug/adverse drug reaction (ADR) pair is estimated using the Information Component (IC), a tool developed by WHO-UMC to measure the reporting ratio. A positive IC reflects a higher statistical association, while negative values indicate a lower statistical association. The IC result for this drug/ADR combination was 5.4, reflecting a positive statistical association.^[3]



Literature: The Signal Detection Team reviewed regulatory sources and published literature to identify evidence linking leflunomide to the risk of rheumatoid lung. The review identified regulatory recognition of this potential risk across multiple authorities^{[4]-[8]}, as well as published systematic review supporting an association between leflunomide and interstitial lung disease.^[9]

Conclusion

The cumulative weight of evidence identified from global cases, literature, and disproportionality analysis suggests a potential causal association between leflunomide and rheumatoid lung. Healthcare professionals and health regulators should be aware of this potential risk in patients receiving leflunomide.

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- National Library of Medicine (NIH) (2024) Leflunomide: MedlinePlus drug information. <https://medlineplus.gov/druginfo/meds/a600032.html>
- 2- National Library of Medicine (NIH) (2025) Rheumatoid lung disease: MedlinePlus Medical Encyclopedia. <https://medlineplus.gov/ency/article/000113.htm>
- 3- VigiLyze (no date). <https://vigilyze.who-umc.org/>
- 4- Food and Drug Administration (2024) Leflunomide label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020905s033lbl.pdf
- 5- European Medicines Agency (EMA) (no date) SUMMARY OF PRODUCT CHARACTERISTICS. https://www.ema.europa.eu/en/documents/product-information/leflunomide-ratiopharm-epar-product-information_en.pdf
- 6- Saudi Food and Drug Authority (2021) Specific safety information. https://www.sFDA.gov.sa/sites/default/files/2021-08/Arava%28leflunomide%29_EducationMaterialforHCP_KSA_draft.pdf
- 7- Medicines and Healthcare products Regulatory Agency (2024) SUMMARY OF PRODUCT CHARACTERISTICS. <https://mhra.products4853.blob.core.windows.net/docs/9a87bba76faa1c3b99c162da03bdf4874a10823b>
- 8- Health Canada (2018) PRODUCT MONOGRAPH INCLUDING PATIENT MEDICATION INFORMATION. https://pdf.hres.ca/dpd_pm/00072390.PDF
- 9- Raj, R. and Nugent, K. (2013) 'Leflunomide-induced interstitial lung disease (a systematic review).', PubMed, 30(3), pp. 167–76. <https://pubmed.ncbi.nlm.nih.gov/24284289>.