



IMPORTANT MEDICINES SAFETY INFORMATION

02 March 2021

Dear Healthcare Professional

RE: RISK OF DRUG INDUCED LIVER INJURY ASSOCIATED WITH THE USE OF METAMIZOLE-CONTAINING MEDICINES

Sanofi-Aventis South Africa (Pty) Ltd and Adcock Ingram Ltd in agreement with the South African Health Products Regulatory Authority (SAHPRA) would like to inform you about the risk of drug induced liver injury (DILI) associated with the use of metamizole-containing medicines.

The Professional Information (PI) and Patient Information Leaflet (PIL) of metamizole-containing medicines will be updated to appropriately reflect the above safety information.

Background on the safety concern

Metamizole is a non-opioid pyrazolone derivative with analgesic, antipyretic and weak anti-inflammatory properties.

Recently identified new information on liver injury prompted a full review of data in association with the potential of metamizole to cause DILI. During the review, we considered information



from all available sources as well as European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) assessment.

Liver injury was observed to be predominantly of a hepatocellular pattern with an onset of a few days to months following treatment initiation with metamizole-containing medicines. Signs and symptoms included elevated serum hepatic enzymes with or without jaundice, frequently in the context of other drug hypersensitivity reactions (e.g., skin rash, blood dyscrasias, fever and eosinophilia) or accompanied by features of autoimmune hepatitis. There are cases reporting liver injury recurrence upon re-administration..

The mechanism of metamizole-induced liver injury is not clearly elucidated, but available data indicate an immuno-allergic mechanism. In general, metamizole-containing medicines induced liver injury may progress to potentially serious outcomes, such as acute hepatic failure requiring liver transplantation.

Advice to healthcare professionals

- Early recognition of potential liver injury from the use of metamizole-containing medicines is essential.
- Patients should be advised to look out for symptoms of potential liver injury and be encouraged to stop the use of metamizole-containing medicines and consult a healthcare professional if such symptoms arise. Symptoms may include right upper quadrant pain, persistent nausea and a complaint of yellow sclera.
- Healthcare professionals are advised to assess and monitor liver function in patients presenting with signs and symptoms suggestive of any liver injury.
- Re-exposure to metamizole-containing medicines is not recommended where no other cause of liver injury has been determined.



- Healthcare professionals are urged to report any adverse reactions (ADRs) or product quality issues to SAHPRA via the eReporting link available on the SAHPRA website (www.sahpra.org.za). Alternatively, please complete the ADR reporting form from the Essential Medicines List (EML) Clinical Guide to report ADRs or product quality issues.
- For more information on ADR reporting of metamizole-containing medicines listed below, please contact the SAHPRA vigilance unit at pvqueries@sahpra.org.za or alternatively use the contact details below:

Table 1: Metamizole-containing medicines

Company	Product Name	Active Ingredients	Registration Number	Contact Details
Sanofi-Aventis South Africa (Pty) Ltd	Buscopan Compositum Tablets	Hyoscine Butylbromide 10 mg Metamizole 250 mg	E/11.2/502	<u>Tel:</u> +27 11 256 3700
	Buscopan Compositum Injection	Hyoscine Butylbromide 20 mg Metamizole 2,5 g	E/11.2/504	<u>Email:</u> za.drugsafety@sanofi.com or ZA.CHCenquiries@sanofi.com
Adcock Ingram Limited	Scopex Co Tablets	Hyoscine-N- butylbromide 10mg Metamizole sodium 250mg	B 1255 (Act 101 of 1965)	Tel: 011 635 0134 Fax: 086 553 0128



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Yours faithfully

GRAEME JAMES

Responsible Pharmacist

Sanofi-Aventis South Africa (Pty) Ltd

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by Tammy Chetty
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Tammy Chetty

Responsible Pharmacist

Adcock Ingram Limited

References

Sabine Weber, et al: Further evidence for the hepatotoxic potential of metamizole, Br J Clin Pharmacol. 2020;1–2.

Marcial Sebode et al: Metamizole: An underrated agent causing severe idiosyncratic drug-induced liver injury, Br J Clin Pharmacol. 2020;86:1406–1415.

Philipp Krisai, Deborah Rudin, David Grünig, Kathrin Scherer, Werner Pichler, Luigi Terracciano and Stephan Krähenbühl: Acute Liver Failure in a Patient Treated With Metamizole, Frontiers in Pharmacology September 2019 | Volume 10 | Article 996

Mathias Lutz,MD: Metamizole (Dipyrone) and the Liver: A Review of the Literature The Journal of Clinical Pharmacology 2019, 59(11) 1433–1442

M. SABATE et al; Risk of acute liver injury associated with the use of drugs: a multicentre population survey Aliment Pharmacol Ther 25, 1401–1409