Metamizole: Risk of drug-induced liver injury

Dear Healthcare Professional,

Representative office of Actavis International (Republic of Malta) in Armenia (hereinafter - the "Company"), which is a member of the group of companies "Teva", where the ultimate parent company is "Teva Pharmaceutical Enterprises Ltd." Marketing authorization holder of metamizole-containing medicinal products Sedalgin Plus and Spasmalgon in agreement with the European Medicines Agency (EMA) and the "Scientific centre of drug and medical technology expertise after academician Emil Gabrielyan" CJSC would like to inform you of the following:

Summary

- **Cases of drug-induced liver injury (DILI) with metamizole have been reported**
- **Advise patients:**
    - **on how to recognise early symptoms suggestive of drug-induced liver injury,**
    - **to stop the use of metamizole should such symptoms occur, and to seek medical assistance in order to assess and monitor liver function.**
- **Metamizole should not be reintroduced in patients with an episode of hepatic injury during treatment with metamizole, for which no other cause of liver injury has been determined.**

The labelling information contained in sections 4.4. ("Warnings and precautions") and 4.8 ("Adverse reactions") of the Summary of Product Characteristics (SmPC) as well as the Package Leaflet of the following products Sedalgin Plus and Spasmalgon will be updated accordingly.

Background on the safety concern

Metamizole is available in fixed combinations such as **Sedalgin Plus** (metamizole sodium, caffeine, thiamine hydrochloride) is indicated from 12 years for the indication of the symptomatic treatment of pain in:

- headache (migraine, tension headache);
- inflammatory and degenerative diseases of the musculoskeletal system;
- postoperative conditions;
- diseases of the peripheral nervous system (radiculitis, plexitis, neuritis, neuralgia, polyneuritis, polyneuropathy);
- menstrual pain.

Spasmalgon (metamizole sodium, pitofenone (pitofenone hydrochloride), fenpiverinium bromide) is indicated from 9 years for the indication of symptomatic treatment of pain syndrome of mild or moderate severity caused by spasm of smooth muscles of internal organs:

- kidney stone disease and inflammatory diseases of the urinary tract, accompanied by pain and impaired urination;

- gastric and intestinal colic, cholelithiasis, biliary dyskinesia;

- painful menstruation.

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, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) considered information from all available sources including adverse drug reaction reports and studies published in the scientific literature.

Liver injury was observed to be predominantly of a hepatocellular pattern with an onset of a few days to months following treatment initiation. 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. In some patients, liver injury recurred upon re-administration.

The mechanism of metamizole-induced liver injury is not clearly elucidated, but available data indicate an immuno-allergic mechanism.

In general, drug-induced liver injury may progress to potentially serious outcomes, such as acute hepatic failure requiring liver transplantation.

Based on the cumulative marketing experience with metamizole of almost 100 years and the extent of patient exposure to the medicine, the occurrence of liver injury due to metamizole is thought to be very rare, but the exact frequency cannot be calculated.

Early recognition of potential liver injury from metamizole use is essential. Patients should be educated to be vigilant for symptoms of potential liver injury and be encouraged to stop the use of metamizole and see a doctor if such symptoms arise. 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 is not recommended in case of a prior liver injury episode that occurred during metamizole treatment, for which no other cause of liver injury has been determined.

Call for reporting

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system on website www.pharm.am or by hotline: (+374 10) 20-05-05, (+374 96) 22-05-05

or Company's email: Safety.Armenia@tevapharm.com

Company contact point

- Should you have any question or require additional information, please report to email: Info.Armenia@tevapharm.com