Direct Healthcare Professional Communication

Metamizole: Risk of drug-induced liver injury

Dear Healthcare Professional,

Marketing authorisation holders of metamizole-containing medicinal products in agreement with the European Medicines Agency (EMA) and the <National Competent Authority> 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 are being updated accordingly.

Background on the safety concern

Metamizole is a non-opioid pyrazolone derivative with potent analgesic, antipyretic and weak anti-inflammatory properties, <which is indicated from 3 months of age in patients weighing at least 5 kg for the treatment of severe or resistant pain and fever. > *[As indications may differ depending on the locally approved label and medical practices, adjust nationally as necessary]*

<Metamizole is also available in fixed combinations such as <active substances of the combination> for the indication of <approved indications>. > *[Complete nationally as necessary]*

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: <if applicable details on the national reporting system.>

Company contact point

- Should you have any question or require additional information, please call Medical Information at < insert contact details of MAHs' local representatives>.

<If applicable: contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substances	Various. Metamizole and fixed combinations of: • Metamizole, caffeine • Metamizole, caffeine, drotaverine hydrochloride • Metamizole, fenpiverinium bromide, pitofenone hydrochloride • Metamizole, hyoscine butyl bromide • Metamizole, pitofenone hydrochloride • Metamizole, triacetonamine tosilate
Marketing authorisation holder(s)	Various. The decision to disseminate the DHPC, as agreed by PRAC, is reverted to each National Competent Authority. In member states where dissemination of the DHPC is deemed necessary, it is strongly encouraged that a single consistent message is sent to healthcare professionals. All concerned marketing authorisation holders are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated. It is encouraged that the originator marketing authorisation holder (SANOFI) acts as the contact point, on behalf of marketing authorisation holders in member states where any of the innovator's products are authorised.
Safety concern and purpose of the communication	To raise awareness of prescribing physicians on the risk of drug-induced liver injury with metamizole use and to prevent inadvertent re-exposure in those who developed liver damage during metamizole treatment
DHPC recipients	Prescribing physicians and those who may diagnose DILI, including general practitioners, oncologists, rheumatologists, internal medicine, surgeons, dentists, orthopaedists, paediatricians, neurologists Hospital pharmacists In countries where metamizole-containing medicinal products are available OTC: community pharmacists DHPC recipients may be agreed at member state level based upon indications and national healthcare system settings under which metamizole is used.
Member States where DHPC will be distributed	In all EEA member states where metamizole-containing medicinal products are on the market, as decided at NCA level.

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	**29 October 2020**
DHPC and communication plan (in English) agreed by CMDh	**12 November 2020**
Submission of translated DHPCs to national competent authorities for review	**20 November 2020**
Agreement of translations by national competent authorities	**30 November 2020**
Dissemination of DHPC	**15 December 2020**