boletim de FARMACOVIGILÂNCIA

VOLUME 25
NUMBER 1
JANUARY 2021

Metamizole
liver injury

Quick Read

- Though probably very rarely, liver injury can occur in association with metamizole (dipyrone) days to months after the start of treatment.
- A pharmacokinetic interaction by enzymatic induction between metamizole and cytochrome CYP2B6 and CYP3A4 substrates can cause a reduction in the plasma concentration of drugs such as bupropion, efavirenz, methadone, valproate, ciclosporin, tacrolimus or sertraline, potentially decreasing their efficacy.

Metamizole (or dipyrone) is a non-opioid pyrazolone derivative. It is a potent analgesic and antipyretic with weak anti-inflammatory properties. It is indicated in acute and intense pain, including spasmodic and tumoral pain, as well as in high fever that is not responsive to other antipyretic therapies.

The European Medicines Agency (EMA) has conducted an assessment of new safety information regarding metamizole, including cases of **Drug Induced Liver Injury (DILI)**. This safety review encompassed data from clinical trials, published case studies, case series and spontaneous adverse drug reaction reports. Instances were identified of causality that was deemed probable; there was also one case of recurrence following rechallenge with metamizole.

The type of liver injury observed was mostly hepatocellular, starting **a few days to months after treatment** initiation. It was usually accompanied by manifestations of drug hypersensitivity or presented features that simulated autoimmune hepatitis. Although the mechanism of liver injury has not been clearly identified, available data point to an immunoallergic pathophysiology.

Data from the cases and the existence of a plausible biological mechanism have led to the relation between metamizole and induced liver injury to be considered as at least reasonably possible. EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has therefore issued a recommendation for the information of metamizole-containing products to be updated and a Dear Healthcare Professional Communication (DHPC) to be disseminated by the Marketing Authorisation Holders.

Cont'd ▶

INDEX CARD

Director: Fátima Canedo
Editor: Rui Pombal
Contributors: Adriana Gamboa, Ana Severiano, Ana Sofia Martins, Cristina Mousinho, Fátima Bragança, Fátima Hergy, Magda Pedro, Márcia Silva, Patrícia Catalão, Sílvia Duarte
Publishing Assistant: Inocência Pinto
Advisory Board: Conselho Diretivo do INFARMED, I.P.
INFARMED – Autoridade Nacional do Medicamento e Produtos de Saúde, I.P.
Parque de Saúde de Lisboa, Av. do Brasil, N.º 53, 1749-004 Lisboa
Phone: +351 217 987 100
E-mail: farmacovigilancia@infarmed.pt
Design and production: Letras & Sinais, Comunicação e Imagem, Lda.
ISSN: 0873-7118

Metamizol: Lesão hepática

▶ *Cont'd*

Sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) will now include drug-induced liver injury as a possible adverse reaction of **unknown frequency**, since its incidence cannot be estimated from currently available data. The comparatively small number of cases in relation to the high number of patients exposed to metamizole, which has been marketed for almost one hundred years, suggests that the incidence of liver injury could be **very low**.

Nevertheless, this adverse reaction should not be underestimated, since it is potentially serious and may evolve into acute hepatic failure requiring a liver transplant. Hence the relevance of increasing healthcare professional and patient awareness in order to ensure early recognition of signs and symptoms (e.g., nausea, vomiting, fever, loss of appetite, dark urine, light stool, jaundice, pruritus, rash or abdominal pain). This could avoid inadvertent re-exposure in cases where the patient has had a previous suspected or confirmed episode of DILI with metamizole.

The most recent safety data review included in- and ex-vivo pharmacokinetic data from which cumulative evidence has emerged of a risk of **pharmacokinetic interaction** through enzyme induction between metamizole and cytochromes **CYP2B6 and CYP3A4**. Section 4.5 of the SPC will therefore be updated to highlight the fact that co-administration of metamizole with **bupropion, efavirenz, methadone, valproate, ciclosporin, tacrolimus or sertraline**, can cause these drugs' plasma concentrations to fall and decrease their efficacy – clinical response and/or blood serum levels should be monitored as clinically appropriate.

Rita Amado Dias

The Portuguese National Pharmacovigilance System is counting on healthcare professionals to keep reporting any ADRs that may occur with medicinal products used in the treatment of COVID-19 – see infografic (in Portuguese)

January highlights from the
Pharmacovigilance Risk Assessment Committee (PRAC)

First monthly safety review of the COVID-19 vaccine Comirnaty®

Following PRAC's assessment, the European Medicines Agency (EMA) published its **first COVID-19 vaccine safety update on 29-Jan-2021, namely regarding Comirnaty®**. In order to be granted marketing authorisation, Comirnaty's safety was carefully assessed through large-scale clinical trials that included people older than 75 years.

This safety review is undertaken **on a monthly basis** and the first one has included an assessment of serious allergic reactions (anaphylaxis). **Anaphylaxis** is a possible adverse effect of the vaccine that was already known. The assessment of the reports of suspected cases of anaphylaxis has **not** detected **any new unexpected features**.

Reports of suspected **fatal** adverse reactions were also assessed. These cases occurred in fragile elderly patients. It was concluded that the cause of death was **progression of the underlying pre-existing condition(s)**. In some cases, palliative care had already been started before vaccination took place.

The EMA has asked the Marketing Authorisation Holder to continue monitoring and analysing in detail every case of anaphylaxis and every report of fatal outcomes. Additionally, the safety and efficacy of vaccines against COVID-19 **will keep being monitored** by each member state's pharmacovigilance system and through **independent studies** coordinated by the European authorities. This aims is to promote immediate assessment of any new emerging data whenever necessary, as well as rapid implementation of appropriate measures that will protect the public's health.

Márcia Silva

Guideline on Good Pharmacovigilance Practices Module XVI Revision

Public Consultation until 28th April 2021

The 3rd revision of Module XVI of Good Pharmacovigilance Practices (risk minimisation measures) and of its Addendum II (methods for effectiveness evaluation) will be out for public consultation until the 28th of April 2021

These documents aim to clarify and reinforce the available tools for medicinal product risk minimisation, such as educational materials, communications to healthcare professionals, pregnancy prevention programmes and controlled access programmes, as well as the methods used to study the effectiveness of the implementation of the above measures.

The draft document and the form for comments can be found **here**

Send your comments to:

gvp@ema.europa.eu

Educational Materials published in the Infomed product information webpage

Click on the links.

INN Medicinal product	Target	Materials? Online publication date
Alemtuzumab Lemtrada	**Physicians:** neurology	Guide Prescriber's checklist
	Patients	Guide Alert Card 21-01-2021
Methylphenidate Concerta, Medicebran, Medikinet, Metilfenidato Mylan, Metilfenidato Ratiopharm, Metilfenidato Sandoz, Quasym, Ritalina LA, Rubifen, Rubifen Retard	**Physicians:** paediatrics, neuropaediatrics and psychiatry	Prescription guide Pre-prescription checklist Ongoing therapy monitoring checklist Ongoing therapy monitoring table 23-01-2021
Lutetium Lu 177 dotatate Lutathera	**Patients**	Leaflet 23-01-2021

Compiled by Patrícia Catalão