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Measures to minimise serious outcomes of known side effect with painkiller metamizole

Product information to be updated to raise awareness of known risk of agranulocytosis and facilitate its early detection and diagnosis

On 18 September 2024, the CMDh[1] endorsed the measures recommended by EMA's safety committee, PRAC, to minimise the serious outcomes of agranulocytosis, a known side effect caused by the painkiller metamizole. Agranulocytosis involves a sudden and sharp decrease in granulocytes, a type of white blood cell, that can lead to serious or even fatal infections.

Metamizole-containing medicines are authorised in a number of EU countries for treating moderate to severe pain and fever. The authorised uses vary from country to country, ranging from the treatment of pain following surgery or injuries to the treatment of cancer-related pain and fever.

Agranulocytosis is a known side effect with metamizole-containing medicines that can occur at any time during treatment or shortly after stopping the medicine, and in people who have used metamizole previously without problems. This serious side effect is not related to the dose of metamizole used. Existing measures in place to minimise this risk vary across countries.

The review was started at the request of the Finnish medicines agency, as cases of agranulocytosis were still being reported with metamizole despite the recent strengthening of risk minimisation measures in Finland.

After reviewing data on the risk of agranulocytosis for metamizole, the PRAC concluded that the existing warnings in the product information needed to be updated. The changes are intended to increase awareness of this serious side effect among patients and healthcare professionals and facilitate its early detection and diagnosis.

The committee recommended that healthcare professionals must inform patients to stop taking these medicines and seek immediate medical attention if they develop symptoms of agranulocytosis. These include fever, chills, sore throat and painful sores on the moist, inner body surfaces (mucosa), especially in the mouth, nose and throat or in the genital or anal regions. Patients must remain alert for these symptoms both during and shortly after stopping treatment.

[1] The CMDh is a medicines regulatory body representing the European Union (EU) Member States, Iceland, Liechtenstein and Norway. It is responsible for ensuring harmonised safety standards for medicines authorised via national procedures across the EU.

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If metamizole is taken for fever, some early symptoms of agranulocytosis may go unnoticed. Similarly, when antibiotics are used together with metamizole, these symptoms may also be masked.

If patients develop symptoms of agranulocytosis, a test to measure their levels of blood cells, including the levels of different types of white blood cells, must be done immediately. Treatment must be stopped while awaiting the results.

PRAC also recommended that metamizole must not be used in patients who are at increased risk of, or susceptible to, agranulocytosis. This includes patients who previously experienced agranulocytosis caused by metamizole, or similar medicines known as pyrazolones or pyrazolidines, who have problems with their bone marrow or who have a condition that affects how their blood cells are made or work.

The recommendations follow a review of all available evidence, including data from the scientific literature, post-marketing safety data and information submitted by stakeholders such as patients and healthcare professionals. During the review, PRAC sought advice from an expert group of specialists experienced in pain management, haematologists, general practitioners, pharmacists and a patient representative.

The PRAC concluded that the benefits of metamizole medicines continue to outweigh the risks. However, the product information for all metamizole-containing medicines will be updated with these recommendations. The PRAC recommendations were sent to the CMDh, which endorsed them and adopted its position on 18 September 2024. The European Commission issued a final legally binding decision applicable across the EU on 22 November 2024.

Information for patients

- Agranulocytosis, a sudden and sharp decrease in granulocytes (a type of white blood cell) that can lead to serious or even fatal infections, is a known side effect with metamizole-containing medicines.
- This side effect can occur at any time during treatment or shortly after stopping the medicine, and in people who have used metamizole previously without problems. It is not related to the dose of metamizole used.
- You must remain alert to the onset of symptoms of agranulocytosis, including fever, chills, sore throat and painful sores in the moist, inner body surfaces (mucosa), especially in the mouth, nose and throat or in the genital or anal regions, both during and shortly after stopping treatment with metamizole-containing medicines.
- If you develop these symptoms, stop taking the medicine and seek urgent medical assistance.
- If metamizole is taken for fever, some early symptoms of agranulocytosis may go unnoticed. Similarly, symptoms may also be masked if you are taking metamizole together with an antibiotic.
- If you develop symptoms of agranulocytosis, your healthcare provider will do a blood test immediately to check your levels of blood cells.
- You must not take these medicines if you have previously experienced agranulocytosis caused by metamizole or similar medicines known as pyrazolones or pyrazolidines, if you have problems with your bone marrow or if you have a condition that affects how your blood cells are made or work.
- The product information of the various metamizole-containing medicines lists agranulocytosis as a rare or very rare side effect, and in some cases a side effect whose frequency is not known.

Although warnings are already in place to minimise this risk, the product information will be updated with more detailed information on how to recognise the symptoms of agranulocytosis and when to consult your doctor.

- If you have any questions or concerns about your medicines, speak with your doctor or pharmacist.

Information for healthcare professionals

- Metamizole-induced agranulocytosis is not dose-dependent and can occur at any time during treatment or shortly following discontinuation, even in patients who have used these medicines previously without complications.
- Patients treated with metamizole must be instructed to discontinue treatment and seek immediate medical attention if they develop symptoms of agranulocytosis and to remain vigilant for these symptoms throughout treatment and shortly following discontinuation, as agranulocytosis may have a delayed onset.
- If metamizole is taken for fever, some early symptoms of agranulocytosis may go unnoticed. Similarly, symptoms may also be masked if metamizole is taken concomitantly with an antibiotic.
- If patients develop symptoms of agranulocytosis, a blood count (including differential blood count) should be performed immediately, and treatment must be discontinued before test results are available. If agranulocytosis is confirmed, treatment must not be reintroduced.
- Routine monitoring of blood counts in patients is no longer recommended as the review did not identify any evidence to support its effectiveness for early detection of metamizole-induced agranulocytosis.
- Metamizole is contraindicated in patients with a previous episode of metamizole-induced agranulocytosis or agranulocytosis induced by other pyrazolones or pyrazolidines, impaired bone marrow function or diseases of the haematopoietic system.
- Warnings are already in place to minimise this risk. However, the product information will be updated to strengthen the existing warnings to raise awareness among patients and healthcare professionals and facilitate early detection and diagnosis of metamizole-induced agranulocytosis.

A direct healthcare professional communication (DHPC) including the above recommendations will be sent in due course to healthcare professionals prescribing, dispensing or administering these medicines. The DHPC is published on a dedicated page on the EMA website.

More about the medicine

Metamizole (also known as dipyrone) is an analgesic medicine (painkiller). It has been used in the EU since the 1920s and is taken by mouth, suppository or injection, to treat moderate to severe pain and fever. The review includes both medicines containing metamizole alone and those containing metamizole in combination with other active substances.

Metamizole-containing medicines are authorised in a number of EU countries: Austria, Belgium, Bulgaria, Croatia, Czech Republic, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg,

Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia and Spain. In Finland, the only authorised metamizole-containing medicine was withdrawn.

They are available under a range of names including Afexil, Algifen, Algifen Neo, Algi-Mabo, Algocalmin, Algopyrin, Algozone, Alindor, Alkagin, Alvotor, Analgin, Benlek, Berlosin, Buscapina Compositum, Dialginum, Dolocalma, Flamborin, Gardan, Hexalgin, Locamin, Metagelan, Metalgial, Metamistad, Metamizol, Metapyrin, Natrijev, Nodoryl, Nofebran, Nolotil, Novalgin, Novalgina, Novalgine, Novaminsulfon, Novocalmin, Panalgorin, Piafen, Piralgin, Pyralgin, Pyralgina, Quarelin, Scopolan Compositum, Spasmalgon and Tempalgin

More about the procedure

The review of metamizole-containing medicines was initiated on 13 June 2024 at the request of the Finnish medicines agency, under Article 107i of Directive 2001/83/EC.

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

The PRAC recommendations were sent to the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh), which adopted its position. The CMDh is a body representing EU Member States as well as Iceland, Liechtenstein and Norway. As the CMDh position was adopted by majority vote, it was sent to the European Commission, which issued a final legally binding decision applicable in all EU Member States.