NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 107i OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 107i of Directive 2001/83/EC to the PRAC made by Finland:

Products (Product Name(s) in the Referring Member State)	Metamizole-containing products (Litalgin 500 mg + 5 mg tablets Litalgin 500 mg/ml + 2 mg/ml solution for injection)
Active substance(s) (Active substances in the Referring Member State)	Metamizole (Metamizole/ pitofenone)
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder in the referring Member State	Takeda Oy

Background

A medicinal product containing metamizole and pitofenone is authorised and marketed in Finland as Litalgin. This medicinal product is authorised as fixed dose combinations (FDC) of 500 mg metamizole + 5 mg pitofenone tablets and 500 mg/ml metamizole + 2 mg/ml pitofenone solution for injection for the therapeutic indications: *Treatment of colic pain in the gastrointestinal tract, biliary ducts and urinary tracts and bladder spasms*. The medicinal product was approved in Finland via a national procedure in 1966 and is available on prescription only. It is formulated for oral, intramuscular and intravenous use. Litalgin is the only metamizole-containing product available in Finland.

Metamizole (also metamizole sodium as per the INN) is a pyrazolone derivate analgesic, which has been marketed since 1922 in Europe as a single agent and in several combination products, indicated in various pain relief indications. The risk of agranulocytosis, defined as a decrease in the blood neutrophil count (neutropenia) to less than 500/μL, has been a known adverse drug reaction (ADR) for metamizole for decades. The reaction can lead to life-threatening and fatal infections. Infections are more likely to occur in some indications for use of metamizole, and therefore the severity of the reactions may also vary depending on indications. Nevertheless, severe reactions may occur in any indication. Due to the risk of agranulocytosis, metamizole-containing products have been withdrawn from the market or refused marketing authorisation in some EU MS and other countries. Metamizole-containing products remain available in 19 EU MS, and are frequently used in some of those. The incidence of agranulocytosis has remained unclear and has varied widely depending on the studies and population. National differences exist regarding measures implemented to minimise this risk. This could be explained by differences in patterns of metamizole use in

terms of indications but it is also suggested that different European populations have dissimilar susceptibility to agranulocytosis caused by metamizole. The exact mechanism of these differences is not known, but it is claimed that the risk may greatly vary between ethnicity (Shah R, 2019). Pitofenone in only authorised in combination with metamizole in the EU.

Following an increasing number of ADR cases of agranulocytosis and serious neutropenia reported to the Finnish ADR registry between 2011-2015 (20 reports, of which 2 fatal), Fimea restricted the use of Litalgin to the shortest period necessary, and prompting for weekly blood count monitoring in case of treatment longer than a week. Furthermore, additional risk minimisation measures were requested nationally to prevent the risk of agranulocytosis in Finnish patients (implemented in 2017: discontinuation of 100-tablet packages, patient alert card, Direct Healthcare Professional Communication letter, Product Information (PI) changes).

Despite the implementation of these additional risk minimisation measures, new cases of agranulocytosis and serious neutropenia were reported (12 reports, of which 2 needed intensive care including intubation and 8 patients were hospitalised for treatment). Therefore, the national measures were further strengthened in 2021 (addition of boxed warnings on the outer packages, SmPC and PL, DHPC letter, addition of information on this risk on the patient alert card).

The reporting rate of agranulocytosis and serious neutropenia, as calculated from spontaneous reports, has been estimated to be one serious spontaneous case in 10,000 – 40,000 users per year in Finland, based on prescription statistics. This calculation might be an underestimate due to limitations related to adverse event recognition and spontaneous reporting.

Issues to be considered

Since the implementation in 2021 of the further strengthened additional measures mentioned above, 7 cases of agranulocytosis and serious neutropenia have been reported in Finland, of which 1 was fatal, 1 led to permanent injury, 1 patient needed intensive care, and 4 patients were hospitalised for treatment.

Based on the content of the case reports, blood white cell counts can decrease very rapidly within a day and only after a few doses of Litalgin. Since Litalgin is used in Finland in acute abdominal colic pains, patients may have an underlying infection causing the pain, which may then develop rapidly into a life-threatening septic infection in case Litalgin decreases the white cell count. In view of the public health impact, Finland considers therefore that the current strict national risk minimisation measures are insufficient to prevent complications related to rapidly developing neutropenia/agranulocytosis specifically, and overall not sufficient to ensure safe use in Finland in the indication of treatment of colic pain in the gastrointestinal tract, biliary ducts and urinary tracts or bladder spasms. The unpredictability and the possibility of a very rapid development (even within a day and only after a few doses) of agranulocytosis reactions hampers the effectiveness of the implemented risk minimisation measures and it is difficult to determine any further feasible risk minimisation measures to ensure safe use, in addition to the already extremely rigorous ones in place in Finland.

While the risk of complications further to metamizole-induced agranulocytosis, may vary depending on indications, and unidentified risk factors, the issue is considered relevant to all metamizole-containing products, including other FDC of metamizole, in their authorised indications.

The above serious safety concern, in the context of the shown lack of effectiveness of the risk minimisation measures in place in Finland, and the difficulty of identifying further risk minimisation measures likely to be effective, leads Fimea to raise concerns about the benefit-risk balance of metamizole-containing products in their authorised indications.

Further, on the basis of these new cases, the MAH of Litalgin considers that the risk of agranulocytosis associated to this product outweighs its benefit, and has taken action to have its marketing authorisation withdrawn. Litalgin is only authorised in Finland.

In view of the above, Finland initiates an urgent union procedure under Article 107i of Directive 2001/83/EC and refers the matter to the PRAC which is requested to give its recommendation as to whether marketing authorisations of metamizole-containing products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the CMDh on the basis of a recommendation of the PRAC.

Signed Date 05 June 2024

Reference:

Shah R, Metamizole (dipyrone)-induced agranulocytosis: Does the risk vary according to ethnicity? 2019 Feb, J Clin Pharm Ther;44(1):129-133

Asiakirjan sähköinen allekirjoitus
Elektronisk underskrift av dokument
Electronic signature of a document

Asia / Ärende / Case:
FIMEA/2024/002924
Selvityspyyntö Takedalle, Litalgin-valmisteiden aiheuttama agranulosytoosiriski

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Allekirjoitukset / Underskrifter / Signatures:

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