Scientific background on the issues leading to the initiation of the procedure on metamizole-containing medicinal products under Article 107i of Directive 2001/83/EC

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Disclaimer:

This assessment report was provided by the Finnish Competent Authority at the time of the initiation of the procedure. It provides background scientific information which complements the final notification request sent by the Finnish Competent Authority for an EU review.

It should be understood that this assessment report reflects the position of the Finnish Competent Authority at the time of the initiation of the referral procedure and is without prejudice to any future position to be established on the matter by the European Medicines Agency through its Scientific Committees.

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. Due to the risk of agranulocytosis, metamizole has been withdrawn from the market or never approved in countries like Sweden France, Norway, UK, USA, Canada and Australia. Metamizole-containing products remain available in 19 EU member states (MSs) 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. The IAAAS study in 1986 initially reported an incidence of 6.2 cases per million per year (1). Further studies in Germany and Spain have supported these findings (2, 3). On the other hand, metamizole was withdrawn from the Swedish market in 1999 based on incidence of agranulocytosis estimated to be at least 1:1439 prescriptions (4). A more recent study from Germany supports the Swedish findings by reporting a risk of 1:1602 for developing drug-induced agranulocytosis and neutropenia after metamizole prescription (5).

National differences exist regarding the measures implemented to minimise the risk of agranulocytosis. 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 ethnicities (6).

Safety data

Finnish spontaneous case reports and national additional risk minimisation measures

Following an increasing number of ADR cases of agranulocytosis and serious neutropenia reported to the Finnish ADR registry between 2011 and 2015 (20 reports, of which 2 fatal), Fimea restricted the use of Litalgin to the shortest period necessary. If, however, Litalgin is used for a longer period, over a week, the blood count of the patient, including differential count of leucocytes, should be monitored on a weekly basis. 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 card, Direct Healthcare Professional Communication letter (DHPC), Product Information (PI) changes).

Despite the deployment of the 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 a boxed warning on the outer packages, DHPC letter, modification of patient card with additional risk information and addition of a boxed warning about agranulocytosis in the beginning of SmPC and PL and highlighting the safety information related to agranulocytosis by a box around the text in the SmPC and PL).

In 2022, Fimea received a report of a very severe case of agranulocytosis leading to permanent sequelae. After this case report, a discussion regarding the effectiveness of the implemented risk minimisation measures was initiated with the MAH and a new DHPC letter was circulated in 2023.

In 2024, Fimea received a fatal case report in which the reaction developed in a day and after only two doses of Litalgin administered as an injection. After this case report, Fimea initiated an assessment of the totality of the Finnish data, including assessment of the effectiveness of the current risk minimisation measures, evaluation of the feasibility of any further risk minimisation measures and considerations regarding the risk-benefit balance of the product.

Overall, 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 involved a patient needing intensive care, and 4 involved patients who were hospitalised for treatment.

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 (meaning at least one 30-tablet package dispensed from a pharmacy within a year) 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.

Based on the content of the case reports, blood white cell counts can decrease very rapidly (within a day) and after only 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 neutropenic septic infection if Litalgin simultaneously causes neutropenia/agranulocytosis. 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 after only 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 rigorous ones in place in Finland.

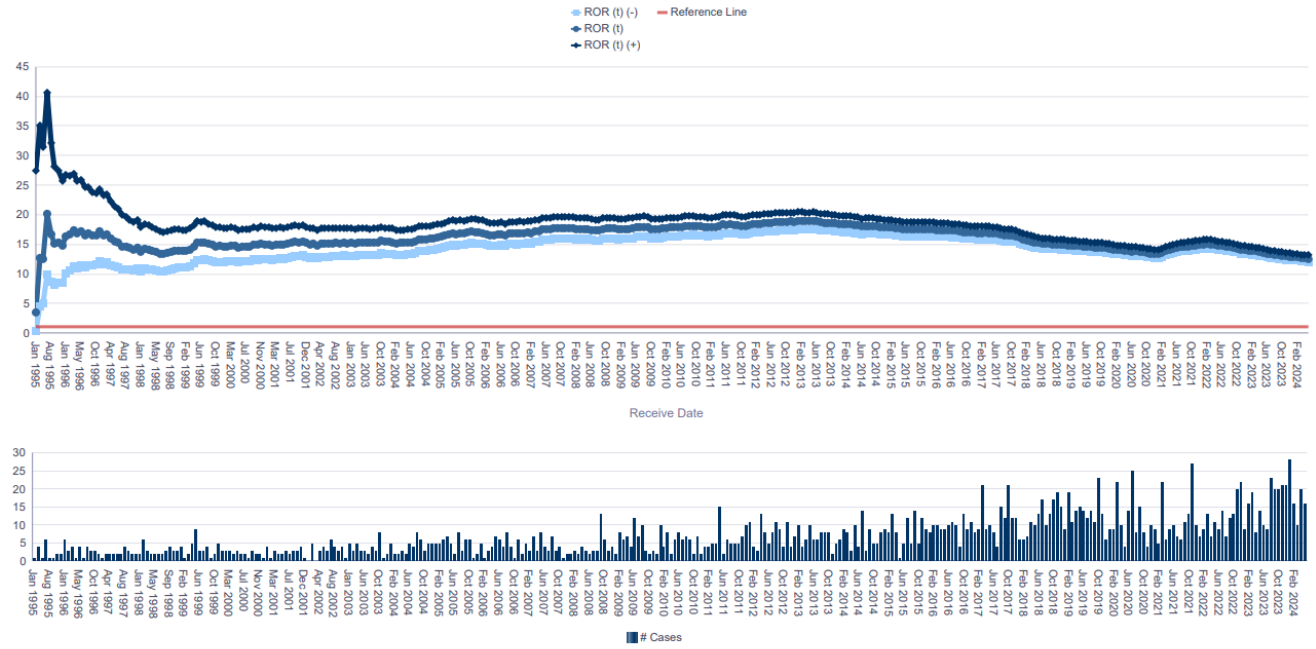
Spontaneous case reports in EudraVigilance

In a published retrospective analysis of the EudraVigilance database from 1985 to 2017, there were 1448 spontaneous reports of suspected metamizole-associated agranulocytosis, of which 16% ended fatally. The median time between starting metamizole and developing an agranulocytosis was 13 days with an interquartile range of 5-34 days, and 34.7% of cases occurred up to 7 days after drug initiation. *This latency time was however much shorter in patients who had already received metamizole before* (with a median of 6 vs 15 days). A total

of 75% of agranulocytoses occurred up to 13 days in patients who had been treated with metamizole before compared to 38 days in those without previous use. Agranulocytoses often resulted in prolonged hospitalisations (75.1%), were categorized as life-threatening in 43.0% and fatal in 16.2% of the reports. The finding that the time between starting metamizole and developing an agranulocytosis was much shorter in patients who had already received metamizole before compared to those without previous use suggests an immunological pathomechanism. However, the precise pathogenesis of metamizole-induced agranulocytosis is poorly understood (7).

Up until 5 June 2024, 2547 events are retrieved from EudraVigilance with the narrow search of the Standardized MedDRA Query (SMQ) for agranulocytosis. The estimated cumulative patient exposure, according to the latest metamizole single component PSUSA (2020-2021) AR, exceeds 25 million patient years (DDD 3000 mg). However, considering the long history of the products, and the fact that PSURs are not required for products referred to Articles 10(1), 10a, 16a of Directive 2001/83/EC as amended, this number is most likely an underestimation.

The figure below shows the dynamic Reporting Odds Ratio (ROR) calculations based on the number of individual cases in EudraVigilance for all metamizole-containing products. A steadily increased ROR and ROR(-) are seen.



Conclusion

The above serious safety concern, in particular in the context of the newly 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 Litalgin-products in Finland.

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

In view of the above, Finland considers that it is in the interest of the Union to refer 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.

Due to action taken by the MAH of Litalgin (withdrawal of national MA due to reason as defined in Medicines Act, section 27, second paragraph) the adequate procedure to evaluate the issue further is a Referral (Article 107i of Directive 2001/83/EC).

References

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