Annex II

Scientific conclusions

Scientific conclusions

Cases of agranulocytosis and serious neutropenia continued to be reported in Finland with the only metamizole-containing medicinal product authorised in this Member State (Litaglin (metamizole/pitofenone)) despite additional risk minimisation measures introduced in 2017, and further strengthened in 2021. This serious safety concern, in the context of the 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, as well as the relevance of this issue to all metamizole-containing medicinal products, led the Finnish National Competent Authority (Fimea) to raise concerns on the benefit-risk balance of metamizole-containing medicinal products.

Furthermore, on the basis of the cases reported after 2021, the marketing authorisation holder (MAH) of Litalgin considered that the risk of agranulocytosis associated with its medicinal product outweighed its benefit and took actions to have its marketing authorisation withdrawn.

On 05 June 2024, the Finnish National Competent Authority (Fimea) triggered an urgent Union procedure under Article 107i of Directive 2001/83/EC, and requested the Pharmacovigilance Risk Assessment Committee (PRAC) to assess the impact of the above concerns on the benefit-risk balance of metamizole-containing medicinal products and issue a recommendation on whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 05 September 2024 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Metamizole is a pyrazolone derivative (anatomical therapeutic chemical [ATC] code: N02BB02) with analgesic, antipyretic and spasmolytic properties. Metamizole-containing medicinal products are authorised in several Member States in the EU and indicated for severe acute and chronic pain, as well as for fever which is not responding to other treatments.

In Finland, following an increasing number of cases of agranulocytosis and serious neutropenia reported to the Finnish adverse drug reaction (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 (DHPC) letter, product information 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, summary of product characteristics (SmPC) and package leaflet (PL), dissemination of a DHPC letter, and addition of information on this risk on the patient alert card). 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. On the basis of these new cases, the MAH of Litalgin (metamizole/pitofenone) considered that the risk of agranulocytosis associated to this medicinal product outweighed its benefit, and took action to have its marketing authorisation withdrawn.

In view of the lack of effectiveness of the risk minimisation measures in place in Finland for Litalgin and the difficulty of identifying further risk minimisation measures likely to be effective, Fimea thus

triggered the present review in order to further investigate the above-mentioned concerns, and their impact on the benefit-risk balance of metamizole-containing medicinal products.

The PRAC reviewed the totality of the data available in relation to the risk of agranulocytosis for metamizole-containing medicinal products. This included responses submitted by the MAHs, data from EudraVigilance, scientific literature, the views expressed by a group of independent experts (ad-hoc expert group (AHEG)), submissions from stakeholders and written intervention received from a third party.

The PRAC considered that the data made available in the context of this referral procedure do not question the established efficacy of metamizole-containing medicinal products. With respect to the risk of agranulocytosis associated with metamizole-containing medicinal products, there is no change in the known nature and magnitude of the risk with the exception of the time to onset (TTO). Based on the available data reviewed, the risk is still considered as rare, whilst it is noted that reported incidences vary widely among different sources as well as geographically. The rarity of metamizole-induced agranulocytosis (MIA) was confirmed in the views shared by the AHEG and stakeholders consulted They indicated that there is overall an extensive experience with metamizole-containing medicinal products (in line with the patient exposure) but only limited experience with this adverse reaction. However, it became clear during the review that agranulocytosis can occur at any time during the treatment and shortly after, in contrast to the previous assumption that the risk is mainly increased after one week of exposure or on long-term treatment reflected in the product information of some metamizole-containing medicinal products.

Overall, the data reviewed indicates that MIA occurs within a short TTO (median of 7-14 days), appearing in the first week of treatment in at least 30-50% of the cases reviewed. An incremental decrease in the number of cases over time was observed. Longer TTOs were observed in subjects receiving metamizole in the outpatient setting versus the inpatient setting. However, precise estimation of latency may be inaccurate due to potential late diagnosis of agranulocytosis and uncertainty in determining the TTOs in cases of intermittent administration. Further, re-exposure of patients to metamizole was associated with shorter TTOs of agranulocytosis. Nevertheless, a considerable proportion of cases with very short latencies were reported without documented previous metamizole use. No adequate data is available to compare risk estimates of short-term versus long-term use or to characterise how the risk changes over time. Analysis of the time course of the reaction also revealed that longer latencies may result from delayed diagnosis due to failure of seeking medical attention on time and are associated with worse patient outcomes. It was also observed that the adverse reaction could occur following uneventful episodes of use of metamizole, which supports the presumed mechanism of immune-mediated agranulocytosis in which previous exposures could sensitize patients and lead to rapid onset of event during further exposures. Additionally, MIA may be detected some time after treatment discontinuation, which may be explained by the pharmacokinetics of metabolites potentially responsible for the reaction, the delay of the immune response directed against granulocytes, an asymptomatic period until the appearance of symptoms of infection, or delays in seeking medical care. In conclusion, based on the data reviewed, MIA is considered a non-dose dependent idiosyncratic reaction, which can occur anytime during treatment and even shortly after treatment discontinuation. The PRAC noted that existing information provided in the product information of some metamizole-containing medicinal products indicates that the risk increases after one week of treatment or on long-term use, which is not substantiated by the evidence reviewed. The PRAC considered that this information should be removed in line with the current knowledge.

In terms of risk factors, there is a lack of scientific multifactorial analysis pointing to independent risk factors for agranulocytosis related to the use of metamizole. Additionally, the review could neither confirm nor refute the assumptions of ethnic differences in susceptibility or the role of underlying infections in more severe outcomes.

The PRAC could however identify patients with poor prognosis of MIA. As described above, MIA is assumed to be an immune-mediated reaction, characterised by the destruction of circulating neutrophils through drug-dependent or drug-induced antibodies or activated T-cells. Immune-mediated reactions are more severe and develop faster upon re-exposure, therefore previous agranulocytosis caused by metamizole and similar substances such as pyrazolones (e.g. phenazone, propyphenazone, isopropylaminophenazone) or pyrazolidines (e.g. phenylbutazone, oxyphenbutazone) in the medical history places these patients in an unacceptable level of risk if metamizole-containing medicinal products are used subsequently. Likewise, if agranulocytosis occurs in patients with already impaired bone marrow function or diseases of the hematopoietic system, these patients are at a higher risk of more severe agranulocytosis and consequently worse outcome. In general, patients with impaired bone marrow function or diseases of the hematopoietic system have been excluded from studies due to potential higher risk of more severe outcomes of agranulocytosis, and consequently from post-marketing studies. The PRAC, whilst noting that similar contraindications are already in place for some metamizole-containing medicinal products, concluded that contraindications for patients with agranulocytosis caused by metamizole or similar substances in the medical history or with existent impaired bone marrow function or diseases of the hematopoietic system should be added to the product information of all metamizole-containing medicinal products.

Delays in seeking medical attention following the appearance of symptoms increases the duration of neutropenia and the likelihood of severe complications of MIA. Therefore, it is critical that healthcare professionals (HCPs) and patients are aware of the early symptoms suggestive of agranulocytosis (e.g. fever, chills, sore throat and painful mucosal changes, especially in the mouth, nose and throat or in the genital or anal region), the importance of immediate discontinuation of treatment should such symptoms emerge, and the need for medical attention as soon as possible without any delay. If metamizole is taken for fever, which can also be a symptom of an emerging agranulocytosis, persistent or recurring fever may be misinterpreted as symptom of the treated condition, and agranulocytosis may go unnoticed. Similarly, some symptoms suggestive of agranulocytosis may also be masked in patients receiving antibiotic therapy. Attention of patients should be drawn to be vigilant in situations when symptoms may be masked or misinterpreted with the treated condition.

The importance of performing a complete blood cell count (including differential blood count) in patients presenting with symptoms suggestive of agranulocytosis should be emphasised for HCPs. Based on the data review, the PRAC concluded that although blood count tests are essential in confirming suspected cases of MIA, there is no evidence to support the effectiveness of existing recommendations for regular blood count monitoring in patients taking metamizole with the aim of the early detection of agranulocytosis to reduce the risk of MIA complications. The routine monitoring currently in place mainly for patients taking metamizole for longer term may not be able to adequately detect cases. This is due to the short latency in a considerable proportion of cases, the sharp decrease of neutrophil count, and the abrupt onset of MIA observed. The lack of support for this measure should be considered together with the described rarity of agranulocytosis and in conjunction with significant patient exposure to metamizole-containing medicinal products. Moreover, the lack of evidence for the effectiveness of routine blood count monitoring was also confirmed by some stakeholder groups that provided input, and by the AHEG, who highlighted the lack of clear scientific data to support such recommendation, and mentioned the burden on patients and healthcare systems routine monitoring may impose. Hence, PRAC concluded that the product information should be updated to remove any reference to regular blood count monitoring of patients under treatment with metamizole-containing medicinal products, as appropriate.

The PRAC noted that national differences exist regarding measures already in place to minimise MIA. It is recognised that these differences can be a reflection of differences between the national healthcare systems, which are in principle a MS prerogative. Whilst further risk minimisation measures were

discussed during the review, the PRAC considered that the early recognition of symptoms and treatment interruption upon their occurrence is critical to minimise the risk of complications of agranulocytosis associated with the use of metamizole-containing medicinal products. This need was supported by the stakeholders who submitted their views as well as the experts of the AHEG consulted during the procedure. Therefore, PRAC recommended the amendments to the product information to convey updated messages in line with the current knowledge to facilitate the prompt recognition and diagnosis of MIA. To support the awareness of the HCPs, a DHPC was also agreed, together with its communication plan.

In view of the above, the Committee considered that the benefit-risk balance of metamizole-containing medicinal products in its authorised indications remains favourable subject to the recommended amendments to the product information.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 107i of Directive 2001/83/EC for metamizole-containing medicinal products.
- The PRAC reviewed the totality of the data available in relation to the risk of agranulocytosis for metamizole-containing medicinal products. This included responses submitted by the marketing authorisation holders (MAHs), data from EudraVigilance, scientific literature, the views expressed by a group of independent experts, submissions from stakeholders and written intervention received from a third party.
- The PRAC noted the established efficacy of metamizole-containing medicinal products in their approved indications.
- The PRAC considered, based on the current knowledge of the established risk of agranulocytosis following the review, that the early recognition of symptoms suggestive of agranulocytosis, treatment interruption of metamizole and prompt clinical testing are critical to minimise the risk of complications of metamizole-induced agranulocytosis.
- Therefore, the PRAC concluded that existing warnings in the product information of metamizole-containing medicinal products needed updating in line with the current knowledge to facilitate prompt recognition and diagnosis of metamizole-induced agranulocytosis.
- Based on the data reviewed, PRAC concluded that there is no evidence to support the effectiveness of existing recommendations for regular blood count monitoring in patients to reduce the risk of metamizole-induced agranulocytosis complications. Metamizole-induced agranulocytosis is not dose-dependent and can occur at any time during treatment and shortly after treatment discontinuation. Blood count monitoring should be performed on suspected cases of agranulocytosis. The PRAC hence concluded that the product information should be updated to remove references to regular blood count monitoring of patients.
- The PRAC also noted concerns about the use of metamizole-containing medicinal products in patients with agranulocytosis caused by metamizole (or other pyrazolones or pyrazolidines) in their medical history, or in patients with existent impaired bone marrow function or diseases of the hematopoietic system, as these patients are at an increased risk of developing agranulocytosis. The PRAC concluded that contraindications in these patient groups should be reflected in the product information of metamizole-containing medicinal products.

In view of the above, the Committee considered that the benefit-risk balance of metamizole-containing medicinal products remains favourable subject to the agreed amendments to the product information.

The Committee, as a consequence, recommended the variation to the terms of the marketing authorisations for metamizole-containing medicinal products.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of metamizole-containing medicinal products remains favourable subject to the amendments to the product information described above.

Therefore, the CMDh recommends the variation to the terms of the marketing authorisations for metamizole-containing medicinal products.