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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 107i of Directive 2001/83/EC

INN/active substance: metamizole

Procedure number: EMEA/H/A-107i/1537

Note:

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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List of abbreviations

ADR	Adverse drug reaction
AHEG	Ad-hoc expert group
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
COX	Cyclo-oxygenase
DHPC	Direct healthcare professional communication
EEA	European Economic Area
EC	European Commission
EMA	European Medicines Agency
EU	European Union
EV	EudraVigilance
G-CSF	Granulocyte colony-stimulating factor
HCP	Healthcare professional
HLA	Human leukocyte antigen
HLGT	High Level Group Terms
IAAAS	International Agranulocytosis and Aplastic Anemia Study
INN	International Nonproprietary Name
MAA	4-methylamino-antipyrine
MAH	Marketing authorisation holder
MIA	Metamizole-induced agranulocytosis
MS	Member state
PG	Prostaglandin
PL	Package leaflet
POM	Prescription-only medicines
PRAC	Pharmacovigilance Risk Assessment Committee
OTC	Over-the-counter
OR	Odds ratio
SmPC	Summary of product characteristics
SMQ	Standardised MedDRA query
TTO	Time to onset

1. Information on the procedure

New cases of agranulocytosis and serious neutropenia continued to be reported in Finland despite additional risk minimisation measures introduced in 2017, which were further strengthened in 2021. In view of the lack of effectiveness of the risk minimisation measures in place in Finland for Litalgin (metamizole/pitofenone) and the difficulty of identifying further risk minimisation measures likely to be effective, the Finnish national competent authority (Fimea) raised concerns on the benefit-risk balance of metamizole-containing products. Furthermore, on the basis of new cases after national measures were further strengthened in 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associated with its medicinal product outweighed its benefit and took actions to have its marketing authorisation withdrawn.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, Fimea therefore 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 to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Metamizole (noramidopyrine-methane-sulfonate, also called dipyrone) is a pyrazolone derivative (anatomical therapeutic chemical [ATC] code: N02BB02) belonging to the group of non-opioid analgesics, with potent analgesic, antipyretic and spasmolytic properties. Metamizole is a pro-drug, the pharmacological effects of which result mainly from the metabolite 4-methylamino-antipyrine (MAA) (Brogden, 1986; Pierre et al, 2007). While its mechanism of action has not been fully understood, it is thought that metamizole may have combined central and peripheral anti-nociceptive effects. Metamizole exerts its analgesic effects through several mechanisms, among which the best described are cyclo-oxygenase (COX) inhibition, activation of the cannabinoid system, and release of endogenous opioid peptides. Metamizole also possesses direct relaxant effect on smooth muscles, resulting in a potent spasmolytic activity that is beneficial in the relief of colicky pain. Some evidence indicates that antipyretic effects of metamizole would come from acting centrally on the hypothalamic heat-regulating centre by inhibiting prostaglandin (PG) synthesis or a step before PG E2 formation. However, and as for antinociceptive action, the antipyretic effect of metamizole could be due to still unidentified mechanisms.

Metamizole has been marketed since 1922 in Europe. Currently, metamizole-containing medicinal products are authorised in 18 member states (MSs) of the European Economic Area (EEA): Austria, Belgium, Bulgaria, Croatia, Czech Republic, Germany, Hungary, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, and Spain. More than 18.5 million patient-years of use could be summed up from MAHs' data for the previous 10 years (2014-2023) presented for metamizole single ingredient products, with Germany and Spain having the largest patient exposure, accounting for 9.96 and 3.16 million patient-years, respectively.

Metamizole-containing medicinal products are available over-the-counter (OTC) in 3 MSs (Hungary, Poland and Bulgaria), while in all remaining MSs they are available as prescription-only medicines (POM). Metamizole is available as monocomponent and in various fixed dose combination products, in which other active substances potentiate the analgesic and/or spasmolytic effect of metamizole. Approved indications of the single ingredient vary between medicinal products and MSs, especially in

indications for pain management. According to the available data, most of metamizole-containing medicinal products have the following indications:

- acute severe pain post-surgery or injury, pain of colic or tumour origin,
- other acute or chronic severe pain, restricted for use only where no other therapeutic options are deemed appropriate / when the use of other medicines is contraindicated or ineffective.

Almost all metamizole-containing products have an indication for fever management as follows:

- high fever, when it is refractory to another treatment / that does not respond to other therapeutic measures including first choice antipyretics.

According to the available data, fixed-dose combination products have in general more specific pain indications and do not contain a fever indication.

Metamizole is indicated in all age groups from infants of 3 months of age or above and weighing at least 5 kg; nevertheless, restrictions may apply depending on the formulation and the indications of the active substance combinations.

Metamizole-containing medicinal products are available in various pharmaceutical forms and strengths for oral (various types of tablets, capsules, oral drops solution, syrup, oral solution, effervescent powder, granules for oral solution, and powder for oral solution), rectal (suppositories) and parenteral (solution for injection) administrations.

The risk of agranulocytosis, defined as a decrease in the blood neutrophil count (neutropenia) to less than $0.5x10^9$/l, has been a known adverse drug reaction (ADR) for metamizole for decades. The reaction can lead to life-threatening and sometimes fatal infections.

The incidence of agranulocytosis has remained unclear due to studies indicating high regional variability, which eventually led to the hypothesis of differences in ethnic susceptibility in the background. A wide variety of national measures has already been in place in the European Union (EU) MSs to mitigate the risk, ranging from information on the risk with relevant warnings and precautions in the product information to controlled access in the Netherlands including prescription restricted to pain specialists, restricted duration of use and pack size and use of educational materials such as a healthcare professional (HCP) guide and a patient card. In some other EU MSs (e.g. France, Norway, Denmark and Sweden), the marketing authorisations of metamizole-containing products were revoked or metamizole was never authorised in some EU MSs (e.g. France, Norway, Denmark and Sweden), due to the risk of agranulocytosis.

In Finland, following an increasing number of 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 (metamizole/pitofenone) 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 product outweighed its benefit, and took actions to have its marketing authorisation(s) 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 for metamizole-containing medicinal products in relation to the risk of agranulocytosis. This included data available in EudraVigilance (EV) as well as the MAHs' responses to the questions from PRAC. The PRAC also considered the outcome of the consultation with an ad-hoc expert group (AHEG), the submissions from stakeholders and a written intervention from a third party.

2.2. Data on safety

Agranulocytosis or acute neutropenia is defined by a neutrophil count of under $0.5x10^9$/l. In most patients, the neutrophil count is observed to be under $0.1x10^9$/l. Patients with such severe neutropenia are likely to experience life-threatening and sometimes fatal infections (Andrès and Maloisel, 2008). Agranulocytosis has been associated with metamizole since the 1940s, and a significant amount of data has accumulated in the past decades to help better understand this rare but potentially life-threatening adverse reaction.

Metamizole-induced agranulocytosis (MIA) is thought to be a type B or idiosyncratic drug reaction. While the pathophysiology is not yet fully elucidated, it has been suggested to be induced either through immunologic or toxic mechanisms, or via the interplay of the two mechanisms. The first mechanism suggests an immune response against granulocytes via antibodies or activated T-cells in the presence of metamizole or a reactive metabolite, leading to their destruction or impaired production (Hargis et al, 1989). This interaction results in severe neutropenia, compromising the patient's immune defence and predisposing them to infections. This theory is supported by studies showing that active metabolites of metamizole function as immunogenic haptens, activating T-cell responses against granulocytes (Johnston et al, 2015; Tesfa et al, 2009; Hargis et al, 1989; Salama et al, 1989).

Recent evidence from *in vitro* studies disagrees with an immune system driven mechanistic hypothesis for MIA, suggesting a direct toxic effect of the main metamizole metabolite MAA, or a complex formed from it, on granulocyte precursors, resulting in their destruction, presumably in the simultaneous deficiency of certain antioxidant mechanisms (Rudin et al, 2019a; Rudin et al, 2019b).

Irrespective of the precise mechanism, some genetic traits influencing the risk of MIA have been suggested, e.g., variations in the major histocompatibility complex, polymorphism of drug metabolising, or key antioxidant enzymes (Tomidis Chatzimanouil et al, 2023).

MIA presents with non-specific symptoms such as fever, chills, sore throat, typically coupled with additional mucosal inflammation, such as aphthous stomatitis, pharyngitis, tonsillitis, or proctitis, all of which may develop into ulcers as the disease progresses. Approximately 60% of reported MIA cases exhibited clinical symptoms and complications such as fever, tonsillitis, pneumonia, and sepsis (Tomidis Chatzimanouil et al, 2023; Johnston et al, 2015).

If MIA is suspected, treatment with metamizole should be immediately stopped and a blood count performed. Moreover, if local or systemic infections occur, as per current clinical guidance for agranulocytosis, immediate diagnostic measures such as blood cultures, swab tests, and infection parameter assessments should be conducted, followed by empirical treatment with broad-spectrum antibiotics. Additional empirical antimycotic therapy and surgical intervention should be further considered. Granulocyte colony-stimulating factor (G-CSF) represents a therapeutic tool, which has frequently been reported in various case reports of MIA. Its administration is generally limited to patients with poor prognostic factors (age over 65 years old, neutrophil count < $0.1x10^9$/l, concomitant use of methotrexate, and severe clinical infection such as bacteraemia, sepsis or shock) (Tomidis Chatzimanouil et al, 2023).

After treatment of MIA, regular blood count monitoring should be performed until normal values are reached. Importantly, patients who previously suffered from MIA should be informed to avoid re-exposure to metamizole (Tomidis Chatzimanouil et al, 2023).

In this review, PRAC conducted a characterisation of MIA in terms of the nature and magnitude of the risk, the time to onset (TTO) and possible risk factors (including genetic or other possible predispositions and the role of underlying infections on the severity and seriousness of agranulocytosis-related complications) as presented in the sections below.

2.2.1. Nature and magnitude of the risk

Reports on MIA show high regional variability on incidence rates. Nonetheless, most of the studies indicate significant association of agranulocytosis with metamizole use versus non-use, with very rare occurrence of the reaction in terms of absolute figures, and a low excess risk. Due to methodological differences and the diversity of data sources and metrics used, risk estimates of MIA are hardly comparable across studies. The studies considered relevant by PRAC are summarised below.

A recent cohort study of new users of metamizole (total of 444,972) performed in the Primary Care Database for Pharmacoepidemiologic Research (BIFAP), a computerized database of anonymized medical records of primary care linked to hospital registries in Spain, calculated an agranulocytosis incidence rate of $8.52/10^7$ person-weeks of use (Maciá-Martínez et al, 2024).

A study published in 2020 analysed data on prescription rates in Germany from statutory health insurance funds and found that among 68.4 million insured persons, 8.1% received at least one metamizole prescription per year. Based on approximately 44 reported cases of agranulocytosis per year from 2015 to 2017 and at least 5.5 million yearly prescriptions in Germany, the data suggested an incidence rate of 7.9 per million prescriptions (Hoffmann et al, 2020b).

Another prospective case-control study from Germany, which included adult patients identified by active surveillance in all 51 Berlin hospitals between 2000 and 2010, reported an incidence of MIA of 0.96 cases per million per year (95% confidence interval (CI) 0.95-0.97) (Huber et al, 2015).

A retrospective study from Poland published based on medical records covering the period 1997-2001 in six haematology centres in Poland, estimated a MIA rate of 0.2 cases per million person-days of use (Maj & Lis, 2002).

A higher absolute risk was reported from Sweden, with incidences calculated in different studies (1 case per 1,439 prescriptions [Hedenmalm and Spigset, 2002]; 1 case per 1,4000 outpatients and 1 case per 31,000 inpatients [Bäckström et al, 2002]; 1 case per 3,000 consumers [Böttiger and Westerholm, 1973]), as well as from one study performed in Germany (1 case per 1,602 prescriptions [Klose et al, 2020]). The figures referred almost exclusively to outpatient use, with some indication that the risk could be lower in the inpatient setting (Böttiger and Westerholm, 1973; Klose et al,

2020). Previously, Ibáñez et al (2005) evaluated 177 community cases of agranulocytosis that were matched to 586 controls in the case-control analysis in Spain. The attributable incidence was 0.56 (95% CI 0.4–0.8) cases per million inhabitants and per year. The first systematic investigation of MIA was performed in the 1980s through the International Agranulocytosis and Aplastic Anemia Study (IAAAS), conducted in Europe and Israel (IAAAS, 1986) reported an incidence of one case per 1,100,000 user weeks or 6.2 cases per million per year.

Furthermore, in a population-based case-cohort study from Netherlands including a large number of subjects from a population of approximately 220,000 to 484,000 persons, the incidence of agranulocytosis leading to hospitalisation was estimated at 1.7 per million inhabitants in 1987, 2.2 per million in 1988, 2.5 per million in 1989, and 1.6 per million in 1990 (van der Klauw et al, 1999). In addition to also being an older study, it is important to note that milder cases were not in its scope.

The European Medicines Agency (EMA) performed during this review a statistical analysis of EV data for cases of agranulocytosis and related terms with metamizole-containing products received from EEA countries over the period between January 2014 and May 2024. All report types (spontaneous, report from studies, other, not available to sender, unknown) were included in the analysis. Only cases where metamizole-containing products were considered suspect/interacting were included in the query. Overall, 1,200 cases were retrieved. Reporting rate was stable over the years. The majority of the cases were reported from Germany (535; 44.6%) and Spain (474; 39.5%), which is in line with the exposure data provided by the MAHs.

In terms of the nature of the risk, the EV analysis (January 2014 – May 2024) performed by the EMA revealed a total of 1,189 serious cases (99.1%), of which 120 (10%) had a fatal outcome. The majority of reactions of interest had resolved or improved at the time of reporting. Cases of fatal agranulocytosis or neutropenia account for 110 of the 120 cases with a fatal outcome. In the remaining fatal cases, causes of death included sepsis/septic shock, multi-organ failure, cancer progression or toxic epidermal necrolysis.

Previously, Hoffman and colleagues (2020) calculated mortality using EV data from 1985 to 2017 and concluded that mortality in regard to MIA is about 16% (Hoffman et al, 2020). Klose et al (2020) performed a real-world cohort study using data from the German insurance claims in the period from 2010 to 2013. It was calculated that 56 (9.5%) patients treated with metamizole and diagnosed with drug-induced agranulocytosis, had died, compared to 8 patients (6.6%) in the control group (i.e., patients diagnosed with agranulocytosis and not exposed to metamizole). However, since no information on the cause of death was provided, results should be considered with caution. The more recent reports indicate lower mortality than previously reported (around 16%), which could potentially be justified by an improvement in detection and treatment of neutropenia/agranulocytosis.

2.2.2. Time to onset

While a wide range of latencies reported in different literature sources (from less than 1 day to several months), the median latency was demonstrated to be between 7 and 14 days, with approximately 30-50% of the reactions appearing in the first week of treatment. The incremental number of cases *per* additional weeks showed a continuous decrease (i.e., the cumulative number of cases as a function of time could be illustrated by a saturation curve, with at least 75% and 90% of cases manifesting up to one month and two months, respectively) (Hoffmann et al, 2020; Blaser et al, 2017; Blaser et al, 2015; Huber et al, 2015; Stammschulte et al, 2015; Hedenmalm and Spigset, 2002). These figures are supported by the analysis of spontaneously reported cases in EV from the EEA, conducted by the EMA concerning the previous 10 years. In this subset, data was available on TTO for 571 cases, which indicated a median latency of 10 days (range: 0 days to 8 years) and 40.2% of cases occurred in the

first week. Still with regards to the EV analysis, median TTO could be analysed by country, which revealed that median TTO was shortest in Spain (8 days) and longest in Finland and 'other countries' (14 days), with Germany in between (11 days).

Several studies have shown that the latency time tends to be shorter in the in-patient setting when compared to outpatients (6 days (1-61 days) and 19 days (2-204 days), respectively) (Rudin et al, 2019c), and in a subset of patients with known previous exposure (median latency of 6 days in previously exposed patients as opposed to 15 days in first users of metamizole) (Hoffmann et al, 2020a). The latter was supported by the EMA EV analysis, which showed that in the 34 cases where metamizole had been used previously, TTO tended to be shorter with a median of 7.5 days (range: 0-28 days) compared with an overall median latency of 10 days, as previously reported.

Nevertheless, in a considerable proportion of cases occurring with a latency of up to one week, no previous exposure was recorded (Hoffmann et al, 2020a). It is uncertain, whether very short onset times in previously unexposed subjects could be inferred from this observation, or if it only reflects incomplete documentation of past metamizole use in spontaneous cases. Precise estimation of latency may be inaccurate due to late diagnosis and uncertainty of determining TTO in cases of intermittent administration.

An analysis of 30 cases from the case-control study of Ibáñez et al (2005) indicated the highest odds of agranulocytosis when treatment lasted for 11-30 days (odds ratio (OR) 167.7, 95% CI 19.6–2,567.7) compared to shorter (for 1 day: OR 14.7, 95% CI 1.4–155.6, for 2-10 days: OR 34.4, 95% CI 3.4–352.1) or longer duration of exposure (for 31-18 days: OR 12.4, 95% CI 1.2–123.3), with wide and overlapping confidence intervals. An increased risk with treatment duration and dose was inferred from higher cumulative doses and treatment periods observed in cases of MIA compared to exposed controls.

Additionally, agranulocytosis was detected following treatment discontinuation (Bäckström et al, 2002; Huber et al, 2015; Blaser et al, 2017). These observations were based on a limited number of cases (<40). Huber et al (2015) identified that in 9 cases (35% of all cases), agranulocytosis developed within 5 days after treatment termination, while no increased risk was demonstrated following 10 days of treatment cessation in the study of Ibáñez et al (2005), and there were only isolated cases from spontaneous reports when latency exceeded this interval.

Notably, from the EV data analysed by EMA during the review, out of 571 cases in the past 10 years where TTO could be calculated, in 180 cases, the onset of agranulocytosis occurred shortly after metamizole was stopped, with a median duration of 3 days (range: 1-359 days) after metamizole withdrawal. In addition, in 172 cases, metamizole was continued after the onset of agranulocytosis, with a median duration of 3 days (range: 1-731 days) after onset, which goes against the current recommendations to discontinue treatment immediately upon occurrence of symptoms.

It was also observed that the reaction could occur following several uneventful episodes of use (Huber et al, 2015). The EMA analysis of EV data showed that a single course of metamizole was reported in most cases (1169 [97.4%]). In 31 cases (2.6%), the patient received two or more courses of metamizole.

2.2.3. Risk factors

Several risk factors have been proposed and investigated within this review, including patient demographics (e.g., age and sex), medical conditions such as autoimmune diseases, history of allergies, or previous leukopenic episodes, viral infections, concomitant medications with a potential to cause agranulocytosis, potential interethnic variations, and genetic risk factors (Radulovic et al, 2021;

Cismaru et al, 2020a; Cismaru et al, 2020b; Rudin et al, 2019a; Rudin et al, 2019b; Rudin et al, 2019c; Shah, 2019; Blaser et al, 2017; Vlahov et al, 1996).

From the comparison of cases with fatal and non-fatal outcome, supported by reviews on non-chemotherapy drug-induced agranulocytosis, poor prognosis is expected with increasing age, low neutrophil counts (below $0.1x10^9$/l), development of severe infections (e.g., sepsis, shock, deep tissue infections), in the presence of serious underlying disease or co-administration of drugs with a potential to depress bone marrow (e.g., methotrexate), or in patients with a previous MIA (Rattay and Benndorf, 2021; Hoffmann et al, 2020a; Blaser et al, 2015; Stammschulte et al, 2015; Andrès and Maloisel, 2008).

Duration and degree of neutropenia are directly proportional to the probability and severity of infectious complications according to the literature, irrespective of the offending agent. Consequently, a longer latency in outpatient cases of MIA was accompanied by lower neutrophil counts and more severe clinical course (Bäckström et al, 2002; Rudin et al, 2019c).

Limited data from case descriptions suggested a role of viral infections including COVID-19 (Lerman et al, 2021) and hepatitis C (Blaser et al, 2017) in increasing the risk of agranulocytosis. Several infections *per se*, as well as antimicrobials used for their treatment are implicated as causative agents of neutropenia and agranulocytosis (Lorenzo-Villalba et al, 2020). Due to the latter two factors, it is difficult to identify the true culprit when metamizole is used in situation of underlying infections.

Moreover, fever could be an indicator of an underlying infection. In the analysis of EV data by Hoffmann *et al* (2020a), fever, as an indication, was more frequently reported among the fatal versus the non-fatal cases (14.4% vs 7.8% in fatal vs non-fatal cases, respectively). Nevertheless, this was not confirmed in the subset analysis of EV data from the previous 10 years reported from EEA countries with verified diagnosis of agranulocytosis, and at least possible causal role of metamizole (4.3% vs 7.5% in fatal versus non-fatal cases, respectively).

Regarding demographic risk factors, overall, higher incidence was reported in women and with increasing age. However, these findings may reflect higher consumption of metamizole in these patient groups (Tomidis Chatzimanouil et al, 2023; Hoffmann et al, 2020a; Blaser et al, 2015; Huber et al, 2015; Stammschulte et al, 2015).

These findings align with the EV analysis conducted by the EMA, gender was reported in 97.7% of cases, with a female predominance (64.3%). In this analysis, the mean age of the patients was 56.8 years (range: 11-93), which is within the adult range. Similar results were found in the EV analysis performed by the EMA, where the mean and median age were 51.7 and 54 years, respectively.

There are no conclusive data from the paediatric population. Nevertheless, due to the rarity of spontaneously reported or solicited cases, the risk is perceived to be lower than in adults (Zahn et al, 2022; Ziesenitz et al, 2018; Blaser et al, 2015; Stammschulte et al, 2015).

In terms of medical history, Blaser et al (2015) reported several possible risk factors for metamizole-associated leukopenia: history of allergies, previous leukopenic episodes, and hepatitis C infection. The EV analysis conducted by the EMA identified a medical history of agranulocytosis (Standardised MedDRA Query [SMQ] Narrow) or haematopoietic leukopenias (SMQ Broad) in 37 cases (3.1%), while a history of allergic conditions (High Level Group Terms [HLGT] multiaxial) was reported in 89 cases (7.4%). Allergy to metamizole or structurally similar compounds is considered plausible by the authors in the light of the presumed immune-mediated mechanism of MIA.

As an idiosyncratic drug reaction, agranulocytosis 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 due to previous sensitisation. Several studies have shown that the latency time tends to be shorter in a subset of patients with known previous exposure (median latency of 13 days in previously exposed patients as opposed to 38 days in first users of metamizole) (Rudin et al, 2019c; Hoffmann et al, 2020a). The latter was supported by the EMA EV analysis, which showed that in the 34 cases where metamizole had been used previously, TTO tended to be shorter with a median of 7.5 days (range: 0-28 days) (compared with an overall median latency of 10 days, as previously reported).

Importantly, aminopyrine, another pyrazolone derivate previously used in the EU for the same indications as metamizole but later revoked due to claims of toxicity and lower level of efficacy, is believed to act as hapten, inducing antibody complexes with neutrophils that lead to their destruction (Chatzimanouil et al, 2023; Leeuw et al, 2017). Cross-sensitivity has been described between metamizole and aminopyrine, suggesting that the risk of agranulocytosis with metamizole may be similar to that of aminopyrine, as well as other pyrazolone derivatives (Chatzimanouil et al, 2023; Leeuw et al, 2017; Brogden, 1986; Miescher et al, 1986). The same may apply also for the related pyrazolidine derivatives, for which agranulocytosis has also been reported (McCarthy et al, 1964; Kennedy et al, 1962).

Additionally, 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.

Finally, genetic predisposition and individual susceptibility are also thought to play roles in the development of drug induced agranulocytosis. In recent years, multiple studies of drug induced agranulocytosis, such as on clozapine, sulfasalazine, and carbimazole, revealed genes associated with increased risk either in the human leukocyte antigen (HLA) region or in other regions involved in immune responses (Cismaru et al, 2020b). Potential evidence on differences in susceptibility of various ethnic groups was reviewed by Shah (2019), triggered by attention of the British and Spanish media concerning British people suffering harm from metamizole obtained in Spain.

Claims of interethnic differences in MIA are based on the IAAAS indicating relevant interregional variability in the relative and absolute risk estimates, and on higher risk estimates documented in Sweden from their national spontaneous reporting system that substantiated the withdrawal of metamizole (IAAAS, 1986; Böttiger and Westerholm, 1973; Hedenmalm and Spigset, 2002; Bäckström et al, 2002).

In search of an explanation, several small-scale exploratory studies aimed at elucidating the potential mechanism of MIA. These studies provided limited evidence on the potential role of variant HLA alleles (Cismaru et al, 2020b; Vlahov et al, 1996), identification of candidate genetic loci implicated in haematopoiesis (Cismaru et al, 2020a), polymorphism of metabolising enzymes (Radulovic et al, 2021), or on direct toxic effect of reactive metamizole metabolites in the presence of hemin and the deficiency of key antioxidant enzymes (Rudin et al 2019a; Rudin et al 2019b).

A retrospective observational case-control study investigating genetic associations with MIA at a genome-wide level in the largest patient cohort available to date could not identify significant genome wide associations and no candidate genes suggesting an immune-mediated mechanism were identified. The authors concluded that these findings thus suggest that the underlying mechanism for MIA may differ from other agranulocytosis-inducing drugs (Cismaru et al, 2020a). Another retrospective study

on the same cohort assessing MIA association with HLA regions concluded that no major HLA risk allele with a strongly increased frequency among patients with MIA or neutropenia was detected, thus making a T-cell-mediated immune mechanism restricted by a specific HLA allele unlikely (Cismaru et al, 2020b).

2.3. Discussion on safety

MIA is a known, rare, and idiosyncratic adverse reaction, non-dose dependent, which may be accompanied by the development of life-threatening infections.

No new data were identified in the current assessment that would lead to a change in the identified nature and magnitude of the risk with the exception of the TTO. Generally, while it can be concluded that the overall risk of MIA is low, there are still uncertainties regarding its exact incidence and underlying pathomechanism.

No changes were observed in the nature or reporting frequency of agranulocytosis in the previous 10 years based on individual cases captured in the MAHs' pharmacovigilance databases or reported to EV. Nevertheless, limitations of spontaneous reporting in delivering precise estimates are noted.

High regional variabilities observed in the risk estimates of MIA have been known for decades, since the results of the IAAAS were first revealed (IAAAS, 1986). This variability may be explained by methodological differences among the various studies (including study design, data sources, case ascertainment, inclusion and exclusion criteria, choice of controls, and definition of exposure relative to the appearance of symptoms / diagnosis), different use patterns, or could reflect true variations in susceptibility of various ethnic groups. The current review was not able to provide a resolution, and clearly support or refute any of the above assumptions. Most studies indicate a very low absolute and high relative risk of metamizole compared to non-use in terms of agranulocytosis. Nevertheless, as reasons behind regional variability remain unknown, no estimates can be provided uniformly applicable for the EEA.

From the data review, MIA occurred with short latency (median of 7 to 14 days), with at least 30-50% of the cases appearing in the first week of treatment, and with an incremental decrease in the number of cases over time. Although re-exposure of patients to metamizole was associated with shorter TTOs, it could not explain a considerable proportion of very short onset cases. Longer latencies were observed in subjects receiving metamizole in the outpatient versus the inpatient setting. However, precise estimation of latency may be inaccurate due to potential late diagnosis of agranulocytosis and uncertainty of determining TTO in cases of intermittent administration.

No adequate data to compare risk estimates of short-term versus long-term use or to characterise how the risk changes over time was identified.

Additionally, it was observed that the reaction could occur following uneventful episodes of use and may be detected shortly after treatment discontinuation (generally up to 5-10 days), which may be explained by the pharmacokinetics of metabolites potentially responsible for the reaction, an asymptomatic period until the appearance of symptoms of infection, or delays in seeking medical care (Blaser et al, 2017; Huber et al, 2015; Bäckström et al, 2002).

Therefore, in view of a significant proportion of cases occurring with short latency, statements about the increase of the risk following one week of use, or on long-term treatment are not considered substantiated with the evidence reviewed. Similarly, the value of the instruction to monitor blood count routinely on longer term therapy, as described in the product information of some products, was considered disputable.

With regards to prognosis, analysis of the time course of the reaction also revealed that longer latencies were associated with worse patient outcomes. Nonetheless, mortality of agranulocytosis has decreased over the last decades from 60% to 2.5–10% which could result from better awareness of the risk, more timely diagnosis and more suitable management (Andrès and Maloisel, 2008). According to the EMA analysis of EV data, agranulocytosis cases are still occurring in which patients fail to seek timely medical attention. Further, data from the scientific literature revealed a degree of non-compliance with the marketing authorisations in terms of approved indication and duration of use. In such cases, metamizole was used for longer periods than recommended in the national label or in conditions of mild pain (Huber et al, 2015; Stammschulte et al, 2015; Huber et al, 2014). Furthermore, longer latencies and more serious cases observed in outpatients were explained by potential delays in recognising the condition, stopping metamizole and seeking medical attendance (Rudin et al, 2019c). This could put such patients at risk of worse prognosis.

No independent risk factors were identified or established in the provided scientific data or in the provided EV analysis. Currently, the available data indicate that genetic predispositions could play a role in the observed different incidences of MIA cases between MSs. Studies on genetic risk factors of MIA provided conflicting results, and due to limitations (specifically from small sample size, exploratory nature of the studies, and only anecdotal evidence available) none of them can be regarded as being confirmed with sufficient evidence (e.g., claims on higher susceptibility of the British population from spontaneously reported cases). Hence, no patient-related genetic or interethnic factors could be identified as a result of the literature review.

Overall, risk factors that may worsen the prognosis of MIA are not specific to metamizole and may be inferred from experience gathered from cases of drug-induced agranulocytosis in general, which is also supported by results of the comparison of fatal versus non-fatal case reports. These include low neutrophil counts, development of serious infections, vulnerability of the patient (e.g., older age, presence of relevant co-morbidities and previous neutropenic episode with metamizole) and concomitant administration of medicines that cause dose-dependent bone marrow toxicity (Rattay and Benndorf, 2021; Lorenzo-Villalba et al, 2020; Andrès and Maloisel, 2008).

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. Since immune-mediated reactions are more severe and develop faster upon re-exposure, as observed in the literature and case reports, previous agranulocytosis caused by metamizole and similar substances such as pyrazolones or pyrazolidines in the medical history places these patients at higher risk of serious outcomes if metamizole-containing medicinal products are used again. Likewise, if agranulocytosis occurs in patients with already impaired bone marrow function or diseases of the hematopoietic system, these patients are also at a higher risk of more severe agranulocytosis and consequently worse outcome. It is noted that for some metamizole-containing medicinal products contraindications are already in place for these patient groups.

2.4. Data on efficacy

No new data became available that would question the efficacy of metamizole-containing products in the approved indications. According to the studies and meta-analyses reported in literature, metamizole is an effective analgesic and antipyretic drug administered for the management of acute and chronic severe and persistent pain or high fever.

3. Expert consultation and stakeholder input

3.1. Ad-hoc expert group meeting

The PRAC consulted an AHEG composed of specialists experienced in pain management, haematologists, general practitioners, pharmacists, and a patient representative, who provided their views on a number of issues. The AHEG answers are presented below.

The experts noted the lack of scientific multifactorial analysis pointing to independent risk factors for agranulocytosis related to the use of metamizole. In the view of the experts, a history of previous MIA, pre-existing conditions (bone marrow depletion, haematological disorders, current infections), prior neutropenia, history of hypersensitivity reactions to metamizole constitute risk factors for MIA. The concomitant use of other medications known to cause agranulocytosis or having an immune- and myelosuppressive effect (e.g. methotrexate) was also noted as an independent risk factor.

As drug-induced agranulocytosis is generally an idiosyncratic reaction, in addition to risk factors, possible poor prognosis for serious complication(s) should be considered in case agranulocytosis develops. As such, the experts consider that particular caution should be exercised when treating the frail population, patients with comorbidities and/or using several medicines (polypharmacy). It was also considered possible by some experts that prior metamizole use may be responsible for the short TTO of MIA seen in some cases.

The experts agreed that there was no data reliably demonstrating possible regional variances of the incidence of MIA. One expert commented on the possibility to explore the conduct of studies to characterise possible ethnical and geographical differences of MIA in order to better inform patients.

As this is a (very) rare reaction, despite extensive clinical experience with the use of metamizole, there was limited experience with the management of MIA amongst the expert group. However, experience can also be drawn from the clinical management of cases of other drug-induced agranulocytosis, which is expected to be aligned. Indeed, in case of symptoms metamizole treatment would be stopped as well as other concomitant treatment suspected to cause or contribute to agranulocytosis and a blood cell count is usually performed as a first step. Most experts highlighted that in case of agranulocytosis they have used or would use an aggressive approach, with prophylactic anti-infective drugs such as broad-spectrum antibiotics, and some would also use G-CSF, along with continuous monitoring and relevant supportive therapy.

In order to minimise the risk of agranulocytosis and its serious complications, the experts considered that the key and primary measure was its early detection. Therefore, the education of both the HCPs and patients on the signs and symptoms of MIA was considered critical. Awareness to those signs was considered all the more critical when metamizole is given as an antipyretic agent, in which case they may be masked by the pre-existing fever.

Overall, the experts highlighted the need for risk awareness and clear information to patients, appropriate patient selection (having in mind the risk factors, comorbidities and polypharmacy) and early detection of symptoms (e.g. fever, sore throat, fatigue, alteration of mucosa (e.g. mouth ulcers)) to stop treatment with medication(s) that could be involved in inducing agranulocytosis.

Patients should also be alerted to delayed agranulocytosis that can occur 1 to 2 weeks after stopping the medication. Some experts shared that in their view that delayed reaction may be due to delayed immune reaction(s) or a delayed detection of symptoms. Additionally, there should be awareness on the clinical aspects to review in case of MIA. The dissemination of a DHPC was suggested to increase awareness on the above.

Additional comments were provided by individual experts. One expert suggested that a patient card could be useful to increase awareness of the risk of MIA and any additional material that could further support HCPs and patients. Another expert suggested a boxed warning in the product information to effectively inform patients, particularly when the medicine is taken OTC. A further expert reflected on the possible usefulness of a concise document with instructions for patients, to support the communication of this information to patients, especially in case of language barriers.

Regarding the need for systematic blood count monitoring tests, the experts noted the lack of clear scientific data supporting its effectiveness in all patients taking metamizole, as well as any specific frequency for such monitoring. Therefore, and considering also that such monitoring is burdensome to patients and healthcare systems, the experts considered that this should be limited to the monitoring of patients presenting signs and symptoms of agranulocytosis.

Outside of the clinical actions, the experts reflected on the access to metamizole, and some expressed the view that these medicines should be restricted to prescription-only, with a minority of experts opposing to this. OTC use was perceived by some experts as inherently riskier, as patients' history is not known to HCPs in sufficient detail and the risk of agranulocytosis may not be communicated appropriately to patients. However, the experts were not unanimous in this respect. One expert suggested that for OTC products, reducing the number of tablets (pack size) could be a measure to take into consideration.

3.2. Stakeholders input

Written submissions were also received from healthcare professionals, healthcare professionals' associations/professional societies, one patient, academia, and industry. All data submitted was considered by the PRAC in reaching its conclusions.

Several stakeholders highlighted that metamizole is important in patients with limited options for analgesia, particularly when alternative treatments are not suitable due to their safety profile. Moreover, metamizole was considered by all stakeholders a safe medicine when used in approved indications. On the other hand, it was suggested that significant off-label use in some countries with high consumption of metamizole could contribute to an increased occurrence of MIA.

Overall, according to the majority of stakeholders' views, the incidence of MIA is generally low. While some stakeholders indicated extensive experience with metamizole-containing products, they reported limited experience with this ADR. Additionally, stakeholders shared published data suggesting different incidence rates according to geographical or ethnic origin.

Stakeholders were of the view that raising awareness amongst HCPs and patients on early recognition of agranulocytosis and immediate discontinuation of metamizole with adequate treatment initiation is vital. Therefore, some stakeholders proposed a DHPC, and a boxed warning in the SmPC and PL. Some stakeholders further suggested that efforts need to be made to reduce unnecessary exposure and off-label use.

The views on the usefulness of laboratory tests of blood count monitoring were split among stakeholders. Stakeholders against the use of such measure considered that this test may come either too early or too late in many cases. Instead, they advocated that focus should be on the early recognition of symptoms.

In addition, a third party submitted a letter expressing their position regarding metamizole. This submission was aligned with the stakeholders' submissions received and did not provide additional information to that presented by the MAHs and other stakeholders.

4. Benefit-risk balance

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

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 EV, scientific literature, the views expressed by a group of independent experts (AHEG), submissions from stakeholders and a 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 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 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 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 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 in 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 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.

5. Summary of new activities and measures

5.1. Risk management

The Committee, having considered all information and data submitted in the procedure, recommended risk minimisation measures to further characterise and minimise the risk of agranulocytosis.

5.1.1. Risk minimisation measures

5.1.1.1. Routine risk minimisation measures

Amendments to the product information

The PRAC considered that routine risk minimisation measures in the form of updates to the product information are necessary in order to minimise the risk of agranulocytosis associated with the use of metamizole-containing medicinal products. These changes include amendments to sections 4.2, 4.3, and 4.4 of the SmPC.

Section 4.2 of the SmPC and/or any other section as applicable should be updated to: remove any existent recommendation on regular blood count monitoring of patients treated with metamizole-containing medicinal products; and to remove any existent text suggesting that the risk is increased after one week or on long-term use.

Section 4.3 of the SmPC should be updated to include contraindications in patients with agranulocytosis in the medical history induced by metamizole, other pyrazolones or pyrazolidines and in patients with existent impaired bone marrow function or diseases of the hematopoietic system.

Section 4.4 should be updated in line with the current knowledge with a boxed warning regarding the risk of agranulocytosis, to facilitate prompt recognition and diagnosis of MIA.

The package leaflet is amended accordingly.

5.2. Direct healthcare professional communication and communication plan

The Committee adopted the wording of a DHPC, to inform HCPs of the risk minimisation measures including the amendments to the product information to minimise the serious outcomes of known risk of agranulocytosis. The Committee also agreed on a communication plan.

All concerned MAHs are encouraged to liaise with national competent authorities to collaborate in order to prepare and circulate a single DHPC in each MS. Nevertheless, and notably in the Netherlands, HCPs are likely to possess a significant level of awareness about the risk of agranulocytosis due to existing controlled access programme currently in place. Therefore, the DHPC content as adopted by PRAC may not add significant value in the current knowledge and awareness on the issue for those HCPs and can be waived in this MS.

6. Grounds for 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 considers 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, recommends the variation to the terms of the marketing authorisations for metamizole-containing medicinal products.

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Appendix 1

Divergent positions to PRAC recommendation

Article 107i of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-107i/1537

Metamizole-containing medicinal products

Divergent statement:

The following PRAC Members consider that the benefit-risk balance of metamizole-containing products is negative, based on the following grounds:

- It is well-established that metamizole causes agranulocytosis, an idiosyncratic and unpredictable adverse reaction that can be fatal due to increased susceptibility to infection and sepsis. Clinical management requires a multidisciplinary approach to optimize patient outcomes.
- Due to this risk, metamizole-containing products have had their marketing authorisations withdrawn or were never authorised in several countries such as France, Norway, Denmark, Sweden, UK, US, Canada, and Australia. In countries where metamizole has remained available, cases of metamizole-induced agranulocytosis with fatal outcomes continue to be reported over time, despite implementation of risk minimization measures. Indications for metamizole-containing products include symptomatic treatment of acute pain and/or fever, however there are other treatment options available for pain and fever.
- The conclusion of a positive benefit-risk mainly rests on assuming that the occurrence of metamizole-induced agranulocytosis is extremely rare. However, uncertainty remains regarding the magnitude of the risk with the estimated incidence varying substantially between regions and studies which may reflect methodological limitations or unidentified genetic susceptibility.
- As no clear risk factors for the reaction have been identified, it is not possible to identify measures that can prevent metamizole-induced agranulocytosis. While 30-50% of cases are reported to occur in the first week, time to onset is widely variable, with cases also reported within a day of starting treatment as well as after treatment discontinuation.
- The PRAC recommendations emphasize the importance of awareness of symptoms to facilitate early detection of metamizole-induced agranulocytosis. However, the symptoms may not appear until the onset of infection, are non-specific, overlap with the indications of metamizole such as fever, and furthermore, may be masked by metamizole. In addition to patient cards, blood count monitoring for treatment beyond one week and reduction of pack size, the risk minimisation measures recommended by the PRAC have already been implemented in Finland but have failed to prevent irreversible complications of metamizole-induced agranulocytosis.

In conclusion, the recommended changes to the product information and the DHPC are not considered sufficient to mitigate the risk of metamizole-induced agranulocytosis or the development of related serious complications across the range of indications for which metamizole is currently authorized.

The benefit risk balance of metamizole is therefore considered negative.

PRAC Members expressing a divergent opinion:

Marie Louise Schougaard Christiansen (DK)

Terhi Lehtinen (FI)

Tiphaine Vaillant (FR)

Rhea Fitzgerald (IE)

Mari Thorn (SE)

Milou-Daniel Drici (PRAC Independent Scientific Expert)

Annalisa Capuano (PRAC Independent Scientific Expert)

Patricia McGettigan (PRAC Independent Scientific Expert)

Hedvig Nordeng (PRAC Independent Scientific Expert)

Anette Kirstine Stark (PRAC Independent Scientific Expert)

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- Due to this risk, metamizole-containing products have had their marketing authorisations withdrawn or were never authorised in several countries such as France, Norway, Denmark, Sweden, UK, US, Canada, and Australia. In countries where metamizole has remained available, cases of metamizole-induced agranulocytosis with fatal outcomes continue to be reported over time, despite implementation of risk minimization measures. Indications for metamizole containing products include symptomatic treatment of acute pain and/or fever, however there are other treatment options available for pain and fever.
- The conclusion of a positive benefit-risk mainly rests on assuming that the occurrence of metamizole-induced agranulocytosis is extremely rare. However, uncertainty remains regarding the magnitude of the risk with the estimated incidence varying substantially between regions and studies which may reflect methodological limitations or unidentified genetic susceptibility.
- As no clear risk factors for the reaction have been identified, it is not possible to identify measures that can prevent metamizole-induced agranulocytosis. While 30-50% of cases are reported to occur in the first week, time to onset is widely variable, with cases also reported within a day of starting treatment as well as after treatment discontinuation.
- The PRAC recommendations emphasize the importance of awareness of symptoms to facilitate early detection of metamizole-induced agranulocytosis. However, the symptoms may not appear until the onset of infection, are non-specific, overlap with the indications of metamizole such as fever, and furthermore, may be masked by metamizole. In addition to patient cards, blood count monitoring for treatment beyond one week and reduction of pack size, the risk minimisation measures recommended by the PRAC have already been implemented in Finland but have failed to prevent irreversible complications of metamizole-induced agranulocytosis.

In conclusion, the recommended changes to the product information and the DHPC are not considered sufficient to mitigate the risk of metamizole-induced agranulocytosis or the development of related serious complications across the range of indications for which metamizole is currently authorized.

The benefit risk balance of metamizole is therefore considered negative.

PRAC Members expressing a divergent opinion:

David Olsen (NO)

Article 107i of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-107i/1537

Metamizole-containing medicinal products

Divergent statement

The below named PRAC Member considers that next to the measures recommended by PRAC, additional risk minimisation measures are required to ensure a positive Benefit/Risk balance of oral formulations of metamizole, based on the following grounds:

- Agranulocytosis is a well-established serious risk of metamizole, which can be fatal. It has an idiosyncratic character, is not dose-dependent, and no risk factors to identify patients at higher risk for developing metamizole-induced agranulocytosis could be identified.
- Symptoms of agranulocytosis are not specific and may be difficult to recognize by patients, as they can be interpreted as general flu-like symptoms.
- Considering the above, in order to ensure a positive B/R balance for the concerned products, oral formulations of metamizole-containing products should be subject to a restricted medical prescription by pain specialist in a hospital setting. In addition, additional risk minimisation measures in the form of educational materials for health care providers and patients are needed to aid early recognition and treatment of the serious risk of agranulocytosis. In order to ensure such restricted use of metamizole, a controlled access program is required.

PRAC Members expressing a divergent opinion:

- Liana Martirosyan (NL)