COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Dolamizol 250 mg and 500 mg tablets (metamizole sodium monohydrate)

NL License RVG: 124159 & 124160

Date: 2 March 2023

This module reflects the scientific discussion for the approval of Dolamizol. The marketing authorisation was granted on 18 March 2021. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
BCS	Biopharmaceutics Classification System
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
COX	Cyclo-oxygenase
DILI	Drug Induced Liver Injury
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FEV1	forced expiratory volume in 1 second
HLA	Human Leukocyte Antigen
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
NSAID	Non-steroidal anti-inflammatory drug
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Medicines Evaluation Board (MEB) of the Netherlands has granted a marketing authorisation for Dolamizol 250 mg and 500 mg tablets, from ALL-GEN Pharmaceuticals & Generics B.V.

The product is indicated for the treatment of strong pains and fever or pains and fever not responding to other treatments, if other treatments are contraindicated.

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

This national procedure concerns a generic application claiming essential similarity with the innovator product Algopyrin which has been registered in Hungary by Sanofi-Avensis cPlc since 2001 (original product). Currently four medicinal products with the same drug substance are authorized in the Netherlands, Metamizol Eureco-Pharma 500 mg/ml, oplossing voor injectie (RVG 117082//04069 and RVG 117084//04069), Metamizol Eureco-Pharma 500 mg/ml, solution for injection (RVG 117084//04069), Metamizol Will-Pharma 500 mg/ml, solution for injection (RVG 114598), and Metamizol 500 mg/ml – solution for injection (RVG 123361//114598).

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

The MAH will supply the following educational material with regards to Dolamizol 250 mg and 500 mg tablets:

The educational material should consist of:

- The SmPC;
- Guide for prescribers;
- Patient card.

Key elements guide for prescribers concerning agranulocytosis:

- The risk of agranulocytosis, its symptoms, its dose independency, its development anytime during the use of this medicine and even after the patient has stopped taking metamizole;
- The risk factor co-medication with methotrexate, the need to avoid re-exposure in patients, and patients at risk (as per SmPC) having previously suffered from metamizole-induced agranulocytosis;
- What to do when agranulocytosis is suspected;
- Importance to inform physician taking over the patient's care after discharge;
- The need to inform the patient and staff about the risk of agranulocytosis and explain the symptoms;
- Ensuring short term (up to two weeks) treatment, initiated by a specialist in pain

treatment in a hospital setting;
- Ensuring that the patient who is treated with oral metamizole will receive the patient card when hospitalized or at discharge.

Key elements Patient card concerning agranulocytosis:
Key elements:
- The risk of agranulocytosis and its symptoms;
- After treatment withdrawal, agranulocytosis and related events may still occur;
- What to do when symptoms of agranulocytosis occur;
- Contact details of the prescriber.

Key elements guide for prescribers concerning drug induced liver injury (DILI):
Key elements:
- The risk of DILI, its symptoms, frequency and seriousness;
- Importance of early recognition of potential liver injury from metamizole use;
- Assessment and monitoring of liver function in patients presenting with signs and symptoms suggestive of any liver injury;
- Patients should be advised on:
  - Importance of recognition of early symptoms suggestive of DILI;
  - Discontinuation of use of metamizole should symptoms of DILI occur, and to seek medical assistance in order to assess and monitor liver function;
- No reintroduction of metamizole in patients with an episode of hepatic injury during treatment with metamizole, for which no other cause of liver injury has been determined.

The MAH shall also ensure a controlled access program
The controlled access program should ensure short term treatment initiated in a hospital setting. Dolamizol supply will be restricted to hospital pharmacies and polyclinical pharmacies. Oral metamizole prescribed by pain specialists in hospitals will not be dispensed by public/community pharmacies.

Plans to evaluate the effectiveness of the interventions and criteria for success:
- The controlled access program will be evaluated by checking at regular times whether the MAH indeed only supplies to hospital pharmacies and polyclinical pharmacies and not to general pharmacies in the Netherlands.
- The effectiveness of the controlled access program can be performed through the outcome of the evaluation of follow-up questionnaires.

II. QUALITY ASPECTS

II.1 Introduction

Dolamizol are tablets, specific appearance information can be found below:

Dolamizol 250 mg tablets:
White, oblong, biconvex tablets with a fracture line on one side and the mark '250' on the other side.

Dolamizol 500 mg tablets:
White, oblong, biconvex tablets with a fracture line on one side and the mark '500' on the other side.

The tablets contain as active substance 250 mg or 500 mg of metamizole sodium monohydrate respectively.

The tablets are packed in white opaque PVC/PVdC/Al blisters in cardboard boxes.

The excipients are corn starch, sodium starch glycolate (type A), povidone K25, magnesium stearate (E470b) and talc (E553b).

The two tablet strengths are fully dose proportional.

II.2 Drug Substance

The active substance is metamizole sodium monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Metamizole sodium monohydrate is a white or almost white crystalline powder. It is very soluble in water. The molecule does not include a chiral centre; stereochemistry issues are not relevant. No data exists on polymorphic forms of the active substance. However, it is shown that the crystal structure of the products is identical to each other in the case of three consecutive manufactured batches.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The drug substance complies with the Ph. Eur. and the CEP. Specifications of the related substances are in accordance with the Ph. Eur. monograph. All specifications and limits are in

line with the Ph. Eur. monograph and CEP. The proposed limits are acceptable. Adequate tests and limits for microbial purity are included. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production batches.

Stability of drug substance

The active substance is stable for three years when stored with no special storage conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

The following development studies were performed; addition, type and/or concentration of binder, glidant, lubricant and disintegrant, particle size and composition of granules. The high solubility of the drug substance at the different pH's is adequately demonstrated as well as the suitability of the analytical method. The MAH requests a Biopharmaceutics Classification System (BCS)-based biowaiver for both tablet strengths based on the facts that metamizole sodium monohydrate is considered not to have a narrow therapeutic index and it is a highly soluble drug with known human absorption. In view of the results for solubility and dissolution, the proposed biowaiver is acceptable from chemical-pharmaceutical point of view. Instead of the normally applied 50 rpm, the MAH uses a higher stirring speed because at 50 rpm a high variation was observed in the first section of the profile of the reference product. The MAH speculates that the high variability is due to the fact that the (flat) tablets stuck at different positions of the vessels. The justification provided by the applicant is considered plausible. The justification supports the use of the higher stirring speed and is in accordance with EMA/CHMP /CVMP/QWP/336031/2017 Reflection paper on the dissolution specification for generic solid oral immediate release products with systemic action: "*A higher stirring speed may be justified by high variability of the results (e.g. > 20% RSD at time-points ≤ 10 minutes, > 10% RSD in the later phase for a sample size of 12) observed at lower speed rates due to hydrodynamic effects (e.g. coning) or other factors (e.g. tablet sticking*)."

At the higher rotation speed, at all pH's both the test and the reference product were dissolved more than 85% in 15 minutes.

Manufacturing process

The manufacturing process is a simple wet granulation followed by compression. A sufficiently detailed description of the manufacturing process is provided in the dossier. Relevant process parameters (e.g. mixing times, mixing speeds, sieve sizes etc.) are included. Internal process controls and hold-time of process-intermediates are considered acceptable. Process validation data on the product has been presented for three pilot scaled batches. The manufacturing process has been adequately validated according to relevant European guidelines. A commitment that process validation data will be submitted for the first three production scale batches has been provided.

Control of excipients
The excipients comply to the Ph. Eur. Requirements for functionality-related characteristics were included for Magnesium Stearate and Talc. These specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, average mass, assay, related substances, uniformity of dosage units, subdivision of tablets, disintegration, dissolution rate, hardness, and microbial purity. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data three pilot scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product have been provided for three pilot scaled batches per strength stored during 48 months at 25°C/60% relative humidity (RH), 12 months at 30°C/65% RH and six months at 40°C/75% RH, in the proposed PVC-PVdC / Alu-blisters in accordance with applicable European guidelines demonstrating the stability of the product for 60 months. The conditions used in the stability studies are according to the ICH stability guideline. Stability data provided supports proposed stability of 60 months with no special temperature storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the MEB considers that Dolamizol has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments were made:

- The specific adverse reaction follow-up forms for the risks of agranulocytosis and DILI will be implemented in Annex 4 of the RMP through a type II variation to be submitted one month after approval of the product.
- The MAH has committed that follow-up forms and the other requested routine pharmacovigilance activities will actually be in place at time of launch of the product in the Netherlands.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Dolamizol is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Algopyrin which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the MEB agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

No bioequivalence study has been carried out on the products (Dolamizol 250 mg and 500 mg tablets) as BCS-based biowaiver has been requested for them on the basis of Appendix III of the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98/rev 1/Corr**). The BCS-based biowaiver approach may represent a surrogate for in vivo bioequivalence, restricted to immediate release drug products with highly soluble drug substances with known human absorption, and considered not to have a narrow therapeutic index.

Biowaiver

The applicant has applied for a BCS-based biowaiver on the basis of Appendix III of the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **) which states that when the test product is an immediate release drug and fulfils all the BCS-based biowaiver requirements, in vivo bioequivalence studies may be waived.

The BCS-based biowaiver approach is meant to reduce in vivo bioequivalence studies, i.e., it may represent a surrogate for in vivo bioequivalence. In vivo bioequivalence studies may be exempted if an assumption of equivalence in in vivo performance can be justified by satisfactory in vitro data.

BCS-based biowaiver are applicable for an immediate release drug product if

- The drug substance has been proven to exhibit high solubility and complete absorption (BCS class I) and;

- Either very rapid (> 85 % within 15 min) or similarly rapid (85 % within 30 min) in vitro dissolution characteristics of the test and reference product has been demonstrated considering specific requirements and;
- Excipients that might affect bioavailability are qualitatively and quantitatively the same. In general, the use of the same excipients in similar amounts is preferred.

It is agreed that the metamizole does not belong to the group of 'narrow therapeutic index' drugs. Additionally it is agreed the excipients of the all strengths of test products are qualitatively identical to the reference products and quantitatively very similar. None of the excipients is expected to affect bioavailability. The applicant showed sufficiently that metamizole is has an almost complete absolute absorption (>85%).

Furthermore, the MAH showed through a solubility study that the active substance is highly soluble and that the maximum single dose fully dissolves in the used medium. Finally, the MAH confirmed through a dissolution study that the active substance and the reference product have similar dissolution profiles. The MAH did use a higher stirring speed than was initially allowed but provided an adequate justification for the use of the higher stirring speed. In view of the results for absorption, solubility and dissolution, the proposed biowaiver is acceptable from a chemical-pharmaceutical point of view.

IV.2 Pharmacodynamics

Metamizole is a prodrug with two pharmacologically active main metabolites, 4-methylaminoantipyridine and 4-aminoantipyridine. In vitro pharmacological study results may not fully correlate with the in vivo pharmacology of metamizole. In common with the NSAIDs metamizole both in vitro and in vivo exerts cyclo-oxygenase (COX)-inhibitory effects and can be regarded a nonspecific COX inhibitor. This, however, as in vivo pain models show, only partially explains its analgesic effect. Beside COX-inhibition metamizole has an influence on oxidative phosphorylation, respiration and adenosine tri phosphate synthesis, participates in redox reactions, is an adenosine tri phosphate sensitive potassium channel opener and relaxant of vascular smooth muscles. Nitric oxide release seems to be the common factor in antinociceptive actions of both morphine and metamizole, although in another study analgesic effect of metamizole was mostly unaffected by naltrexone, suggesting that endogenous opioids were not involved in that model. Glutamatergic-mediated pain responses, specifically those mediated by metabotropic receptor subtype, together with inhibition of neurokinin 1-mediated response, may account for the antinociceptive action of metamizole. Furthermore, activation of the protein kinase C-dependent pathway can also play a role in the antinociceptive action of metamizole. The analgesic effects of Non-steroidal anti-inflammatory drugs (NSAIDs) at the periaqueductal grey matter are at least partly related to endogenous opioids and cannabinoids and in the end indirectly result in an attenuation of gamma-aminobutyric acidergic synapses, thus increasing the activity of output neurons responsible for descending inhibition. Additional mechanisms of action cannot be excluded.

In accordance with in vitro findings on guinea pig trachea smooth muscle relaxing effect of metamizole, this drug had a significant effect leading to an improved small airway function in asthmatic patients with moderate airway obstruction. 22 patients were classified according to their baseline forced expiratory volume in 1 second (FEV1) as having mild obstruction (FEV1 ≥

80% predicted) or moderate obstruction (FEV1 60%-80% predicted). Significant improvement with metamizole was seen in FEV1 and peak expiratory flow rates at 25%, 50% and 75% of forced vital capacity and in maximum mid-expiratory flow rate only in patients with moderate asthma. No significant change was observed on the spontaneous recovery day except in FEV1.

IV.3 Clinical efficacy

For the current application studies in oral metamizole will be assessed. Studies with a randomized, double-blind, placebo-controlled design reflecting the proposed indication and cochrane reviews were considered pivotal studies.

The following studies were dicussed by the MAH in the clinical overview:

Visceral surgery
One study in epistiotomy (Gomez et al. 1980), and a Cochrane review in acute postoperative pain (Edwards et al. 2010) were submitted. Both studies are described in the table above. Gomez concluded that 1000 mg metamizole was more effective than 1000 mg paracetamol and placebo at 30 min, one , two and four hours in moderate to severe episiotomy pain. Rescue medication was not permitted between episiotomy and after six hours, unless there was no pain relief after two hours. No patients in the metamizole group required rescue medication. In the paracetamol group this were three patients and for placebo two. Metamizole was significantly more effective than paracetamol at every assessment up to four hours, in relieving severe pain. For moderate pain this is not repored. After five hours no difference in pain intensity between treatment and placebo was found.

Edwards et al. (2010) concluded that based on very limited information, single dose metamizole 500 mg provides good pain relief to 70% of patients in acute postoperative pain. For every five individuals given metamizole 500 mg, two would experience this level of good pain relief which whould not have been achieved with placebo, and fewer patients would need rescue medication, over four to six hours. However a remark is made that results should be interpreted with caution as they are based on limited information from relatively few patients and estimates might not be robust.

Acute mild, moderate or severe pain (dental surgery, colic pain)
Two randomised controlled trials in dental surgery by Rohdewald et al. (1988) and Planas et al. (1998) were submitted. In the study by Rohdewald electric tooth pulp stimulation was used to simulate acute, moderate to severe pain at different time intervals up to seven hours after drug administration. Metamizole was administered in serveral oral dosages: 0.5 g, 1 g, 1.5 g, 2 g and 2.5 g and placebo. All doses of dipyrone had a significantly higher analgesic effect than placebo. Maximal analgesia was observed one hour after tablet-administration, independent of the dose. A dose response in analgesic effect was observed at this timepoint. However, the increase was less pronounced with doses exceeding 1.5 g metamizole. After five hours a very slight effect of metamizole was observed in pain reduction. At this timepoint, only 1 g and 1.5 g seperated from placebo in pain relief.

Planas et al. (1998) found that in post dental surgery pain (extraction of the lower third molar) 2000 mg metamizole showed more pain relief after one hour than 600 mg ibuprofen.

However, no differences in pain relief between 1000 mg and 2000 mg metamizole was found, moreover pain relief for 1000 mg was comparable with 600 mg ibuprofen. Procedures included type II: molar in the sumbucosa, type III: molar partially included in the bone and type IV: molar fully included in the bone. It was unfortunately not reported how many patients were included for each type and thus the severity of the painmodel studied.

Tumour pain

For tumour pain as a model of chronic moderate to severe pain, reference is made by the Applicant to three studies (Souza et al. 2007, Rodríguez et al. 1994 and Yalcin et al. 1998) and a German guideline (Ladner et al. 2000). Two studies do not contain a placebo arm (Rodríguez et al. 1994 and Yalcin et al. 1998), thus no firm conclusions on efficacy can be made. One double-blind placebo-controlled randomized crossover study investigated metamizole in addition to morphine (Souza et al. 2007). 16 patients were randomised to start with placebo (group 1) and 18 with 500mg metamizole (group 2). After 48 hours, patients were switched to the other treatment. Pain scores for groups 1 and 2 were at baseline: 7.31±0.29 vs 6.88 ±0.28 ($p = 0.3$), at 48 h: 7.06 ±0.32 vs 5.5 ±0.31 ($p = 0.001$), and at 96 h: 3.18 ±0.39 vs 1.94 ±0.37 ($p = 0.03$). Both groups had significant improvements in pain scores after introducing metamizole ($p < 0.001$, for both). It should however be noted that in group 2 the decrease in pain after receiving first metamizole continued on placebo. According to the authors, this implicates that earlier adequate pain control may translate into superior analgesia later.

Other acute or chronic severe pain, where other therapeutic measures are not indicated

Martinez-Martin et al. (2001) investigated metamizole in 417 patients with moderate episodic tension-type headache. Treatment arms were metamizole 0.5 g (n=102), metamizole 1 g (n=108), asperin 1 g (n=102) and placebo (n=105). The analgesic efficacy of 0.5 and 1 g metamizole vs. placebo was significant (α: 0.025; one-sided) for sum of pain intensity differences, maximum pain intensity difference, number of patients with at least 50% pain reduction, time to 50% pain reduction, maximum pain relief and total pain relief. A trend towards an earlier onset of a more profound pain relief of 0.5 and 1 g metamizole over 1 g ASA was noticed. Type and posology of permitted rescue medication was not reported. In addition, in the Cochrane review by Ramacciotti et al. (2007) a comment is made that the results should be considered carefully, since data for most of these continuous outcomes were skewed, except for the comparison between dipyrone g orally and placebo for 'pain relief at two hours'.

Tulunay et al. (2004) studied a single dose 1000 mg metamizole in patients with migraine (a total of three attacks, with 72hours in between the attacks). Pain intensity was measured on a four-point verbal pain scale before and 1, 2, 4 and 24 hours after drug intake. Significant improvement of pain was achieved with dipyrone compared to placebo at all time points. Total pain relief: 1h: metamizole: 21% vs placebo: 2% ($p<0.001$); 2h: metamizole: 38% vs placebo: 11% ($p<0.001$); 4h: metamizole: 40% vs placebo: 13% ($p<0.001$). In the metamizole group, less rescue medication (ergotamine 1mg + metochlopramide 10mg) was needed than in the placebo group (12.5% vs. 42.9%). The drop-out rate was quite high: 20-30%, moslty after the second visit.

High fever that does not respond to other measures
For the indication of high fever that does not respond to other measures, the Applicant refers to three studies in children (Wong et al. 2001, San Bartolomé. 2006 and IMIP. 2008). The study by Wong included paracetamol and ibuprofen as active comparators and had a double-blind, randomized design. Single-doses were 15mg/kg metamizole (syrup), 12 mg/kg paracetamol and 5 or 10 mg/kg ibuprofen (depending on baseline temperature). From 4-6 hours, metamizole was more efficaciuos than ibuprofen and paracetamol in reducing the temperature from baseline. The study by San Bartolomé hospital investigated single doses of oral ibuprofen (10 mg/kg), oral dipyrone (15 mg/kg) and intramuscular dipyrone (15 mg/kg) in febrile children. The results showed similar antipyretic effects from oral ibuprofen, oral metamizole and intramuscular metamizole. The study by IMIP hospital was a randomized trial that investigated the effect of tepid sponging in addition to metamizole treatment and not the efficacy of metamizole in lowering fever.

None of these three studies included a placebo-arm. These studies concluded that metamizole was effective in reducing fever. It should however be noted that the paracetamol dose of 12 mg/kg might be suboptimal in the treatment of fever, normally a maximum dose of 75 mg/kg is considered safe in treatment of fever in (young) children.

IV.4 Clinical safety

IV.4.1 Incidence of metamizol-related agranulocytosis

Published studies reported differences in the magnitude of risk of adverse outcomes associated with metamizole use and often had small sample sizes and a number of other limitations that may have biased the results. So far most analyses of spontaneous reports of agranulocytosis attributed to metamizole were based on data from single countries like Germany, Switzerland or Sweden, did not stratify their analyses by country, or provided differences between fatal and non-fatal cases only for a small number of patients. The incidence of metamizole-associated agranulocytosis remains unclear. Earlier studies on the incidence of metamizole-induced agranulocytosis show wide geographical variation (Hedenmalm et al 2002) for example, ranging from one case per 1439 prescriptions in Sweden (Hedenmalm et al 2002) to one case per 133,000-466,000 treatments in Greece (Varonos et al. 1979).

All metamizole containing products in Sweden were withdrawn in March of 1974 only to be re-introduced in September 1995 and to be suspended once again in April 1999 with different computations and estimates of risk at each time point (Hedenmalm et al 2002). In a study cases of agranulocytosis submitted to the Swedish Adverse Drug Reactions Advisory Committee (SADRAC) between 1996 and 1999 were used. Based on the utilization pattern of metamizole in inpatients at three hospitals and in outpatients in two counties in northern Sweden risk estimates of agranulocytosis during metamizole treatment were estimated. The utilization of metamizole was investigated by scanning 3567 case records at 10 hospital departments as well as stored prescriptions at six pharmacies during a three-month study period. Ten cases of agranulocytosis during treatment with metamizole have been reported to SADRAC over the period 1996 to 1999. During the three-month study period metamizole was prescribed to 666 (19%) inpatients. Of these, approximately 96% received the drug for less than one week, 7.2% had used the drug previously. At the participating pharmacies 112

metamizole prescriptions for outpatients were found. The drug was prescribed in 34% for less than one week, in 28% for seven–15 days, and in 38% for more than 15 days. The mean prescribed daily dose was 2.7 g. Given certain assumptions including the actual amounts prescribed the calculated risks of agranulocytosis would be approximately one out of every 31 000 metamizole-treated inpatients and one of every 1400 metamizole-treated outpatients.

Studies over the last few years from Spain, Switzerland, Germany, Poland and Latin America have reported on the rarity of this serious complication of metamizole therapy (Blaser et al. 2015, Ibáñez et al. 2002, Maj et al. 2002, Basak et al. 2010, Huber et al. 2015, Hamersclak et al. 2008). For example, in 2005, Ibáñez et al reported that the frequency of metamizole-induced agranulocytosis in Barcelona area was <one case per million per year (Ibáñez et al. 2002). The fatality rates vary widely, for example, from 0.6% to 24% (Stammschulte et al. 2015).

Recently a study analysed the spontaneous reports of suspected metamizole-associated agranulocytosis recorded in EudraVigilance database from 1985 to 2017 with regard to patient and treatment characteristics as well as fatal vs non-fatal outcomes and compared these findings among countries. A total of 1448 reports from 31 different countries were included (Germany 42.0%; Spain 29.6%; Switzerland 13.1%; other countries 15.3%). Mean age of patients was 53.6 years (63.4% females). Differences among countries were observed, for example with respect to patient age, route of administration and daily doses. About 16% of cases ended fatally. It was not possible to draw conclusions on the incidence of metamizole-associated agranulocytosis from our study (one).

A recently (Reist et al. 2018) published survey of clinical practice in German-speaking countries provided a link to a questionnaire on the use of nonopioid analgesics (NSAIDs, COX-2 inhibitors, paracetamol, metamizole) and the safety of metamizole in the perioperative and chronic pain setting was mailed to anaesthesiologists and pain physicians. A total of 2237 responses were analysed. About 97.4% of the respondents used nonopioid analgesics for the treatment of acute pain, with 93.8% administering metamizole, 54.0% NSAIDs, 41.8% COX-2 inhibitors and 49.2% paracetamol. Nonopioid analgesics were administered preoperatively by 22.3%, intraoperatively by 86.1% and postoperatively by 73.0% of the respondents. For chronic pain management, 76.7% of the respondents prescribed oral metamizole in combination with other nonopioid analgesics; 19.9% used metamizole as sole nonopioid, whereas 2.9% denied its use.

Metamizole-associated changes in white blood cell counts were reported by 18.3% (386) and 16.4% (153) of the participants engaged in acute and chronic pain treatment, respectively. Leukopenia was observed by about 10% of the respondents in each group. Severe adverse reactions such as agranulocytosis and pancytopenia were more frequently described in the perioperative than in the chronic pain setting. Of those filling in the acute pain questionnaire, 3.5% (74) mentioned an agranulocytosis and 1.7% (35) a pancytopenia in patients under metamizole treatment. The respective figures in chronic pain treatment were 1.5% (14) for agranulocytosis and 1.0% (nine) for pancytopenia. As mentioned, 3.5% of the participants observed an agranulocytosis within a two-year period. At first sight this appears rather high; however, the overall high frequency of metamizole prescriptions puts the absolute number of patients having received metamizole during two years in perspective. Additionally, probably

not all reported cases were in fact caused by metamizole since other reasons must be taken into account, for example other concomitant medicines. Most of the patients with acute or chronic pain receive additional analgesics, for example opioids or co-analgesics, which might also induce side effects (Reist et al. 2018).

According to authors from the Netherlands (Konijnenbelt-Peters et al. 2017), the risk for fatal side effects with metamizole, including agranulocytosis, is estimated to be comparable to paracetamol and much lower than, for instance, in diclofenac, mainly because of lower incidence of gastric ulceration and bleeding (25, 20, and 592 fatalities per 100 million users, respectively) (Andrade et al. 2016). In the Netherlands, each year 1,400,000 operations are performed, 700,000 of which are undertaken during clinical admission. If metamizole would be administered after every clinical operation in which other NSAIDs are contraindicated (assuming a high estimate of 50%), and an agranulocytosis incidence of 1:1,000,000 is assumed (in accordance with the larger case–control studies) with a mortality rate of 15%, in the Netherlands there would be one case of metamizole-induced agranulocytosis every three years, and one death every 20 years (Konijnenbelt-Peters et al. 2017).

Children

Overall, this serious and potentially fatal adverse drug reaction has been rarely described in children. A post authorization safety study in 1177 children did not report any paediatric drug-induced agranulocytosis (Isik et al. 2014). However, drug-induced agranulocytosis in children has been published in case reports (de Leeuw et al. 2018, Isik et al. 2014) and additional cases have been reported to local authorities (Blaser et al. 2015, Stammschulte et al. 2015). In a recent German analysis, six of 161 reported cases (3.7%) of metamizole-induced agranulocytosis occurred in patients aged 11-17 years between 1990 and 2012. (Andrade et al. 2016) In a Swiss retrospective analysis of spontaneously reported metamizole-associated haematological adverse drug reactions between 1991 and 2013, three of 77 reports (3.9%) were in patients younger than 19 years of age (Blaser et al. 2015). No cases of metamizole-induced agranulocytosis with fatal outcome have been reported in children so far.

IV.4.2 Influence of the duration of treatment on metamizole-related agranulocytosis

In a meta-analysis of randomized controlled trials that compared the safety of metamizole to placebo and other analgesics, there was no difference in adverse events between metamizole and placebo, paracetamol, acetylsalicylic acid, or NSAIDs, and fewer adverse events compared to opioids. These 79 trials, which included almost 4000 patients with short-term metamizole use of less than two weeks, reported few serious adverse events, with no difference between metamizole and the comparators, and no cases of agranulocytosis (Kötter et al. 2015). According to EudraVigilance data from 1985 to 2017, overall, median time between starting metamizole and developing an agranulocytosis was 13 days with 34.7% of cases occurring up to seven days. This time was much shorter in patients who had already received metamizole before (median: six vs 15 days) (Hoffman et al. 2019).

IV.4.3 Patients at increased risk of metamizol-related agranulocytosis

According to EudraVigilance data from 1985 to 2017, patients with fatal outcomes were older and more often had also received methotrexate compared to those with non-fatal outcomes. When adjusting for age and sex in a multivariable logistic regression, methotrexate was

associated with an increased risk of fatal outcomes (odds ratio: 5.18; 95% confidence interval: 3.06-8.78) (Hoffman et al. 2019).

A German study aimed to evaluate prescribing of metamizole in Germany with respect to age, sex and regional variations. Using data of a statutory health insurance, we analysed a cohort of 1.7 million persons who were insured at least one day in each quarter of 2009. Outcome of interest was the outpatient prescription prevalence, for example the proportion of persons receiving at least one prescription of metamizole (Hoffman et al. 2015). It is significant, because these results (see in table 1 below) may show what usage pattern to expect in the Netherlands from ten years of age up to the elderly.

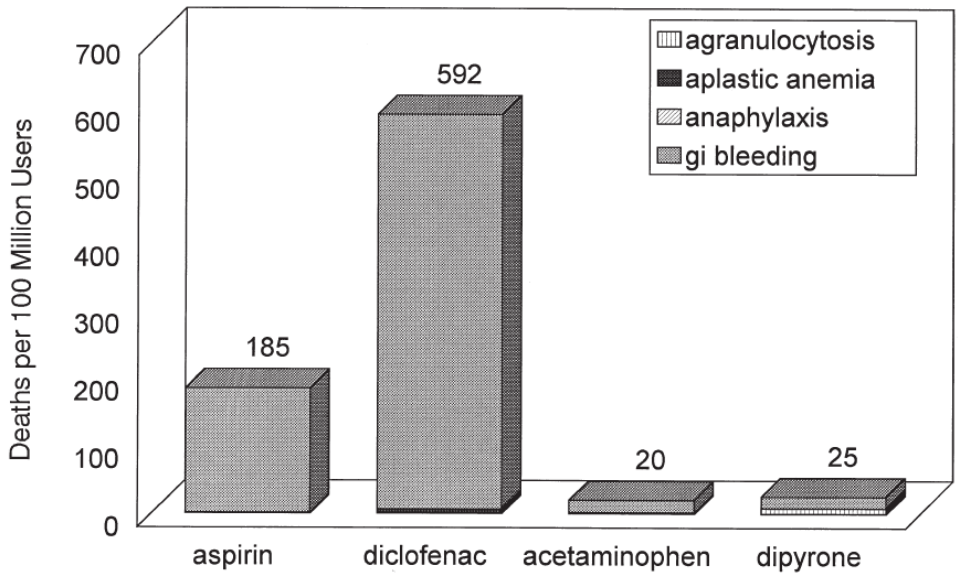
Table 1. Prescription prevalence's of metamizole with 95% confidence intervals (95% CI), by sex and age group (Hoffman et al. 2015).

	Males (%) (95% CI)	Females (%) (95% CI)	Total (%) (95% CI)
0–6 years (n = 89 483)	0·4 (0·3–0·4)	0·3 (0·3–0·4)	0·4 (0·3–0·4)
7–10 years (n = 71 314)	0·6 (0·5–0·7)	0·6 (0·5–0·7)	0·6 (0·5–0·7)
11–13 years (n = 58 274)	1·7 (1·5–1·8)	1·8 (1·7–2·0)	1·7 (1·6–1·8)
14–17 years (n = 79 182)	3·7 (3·5–3·9)	5·7 (5·4–5·9)	4·7 (4·5–4·8)
18–34 years (n = 355 138)	4·8 (4·7–4·9)	6·9 (6·7–7·0)	5·9 (5·8–5·9)
35–44 years (n = 278 148)	5·8 (5·7–5·9)	7·3 (7·2–7·4)	6·5 (6·4–6·6)
45–54 years (n = 318 694)	6·4 (6·3–6·6)	8·4 (8·3–8·6)	7·4 (7·3–7·4)
55–64 years (n = 197 504)	8·1 (7·9–8·2)	10·1 (9·9–10·3)	9·0 (8·9–9·1)
65–74 years (n = 146 241)	9·1 (8·9–9·3)	12·9 (12·6–13·2)	10·7 (10·5–10·8)
75–84 years (n = 55 253)	14·2 (13·8–14·6)	20·9 (20·4–21·4)	17·2 (16·9–17·6)
85+ years (n = 10 947)	21·1 (19·9–22·3)	30·4 (29·3–31·5)	26·7 (25·9–27·5)
Total (n = 1 660 178)	6·0 (5·9–6·0)	7·8 (7·8–7·9)	6·8 (6·8–6·9)

Preliminary evidence also suggests that the presence of specific variant human leukocyte antigen (HLA) alleles may sensitize individuals to metamizole-induced agranulocytosis. The possibility that the British, Irish and Scandinavians show higher susceptibility than other populations to metamizole-induced agranulocytosis cannot be ruled out. If this complication is linked to specific HLA allele(s), populations with higher frequency of variant HLA allele(s) may be at a greater risk. If confirmed, screening for the risk allele may be useful in reducing the risk of metamizole-induced agranulocytosis (Shah RR. 2019).

Last but not least, one has to look at the general comparative safety characteristics of minor analgesics. A study identified epidemiologic studies, published from January 1970 to December 1995, that investigated the association of serious adverse effects with acetylsalicylic acid, diclofenac, paracetamol, and metamizole to determine and compare the excess mortality associated with short-term drug use. The estimated excess mortality due to community acquired agranulocytosis, aplastic anaemia, anaphylaxis, and serious upper gastrointestinal complications was 185 per 100 million for acetylsalicylic acid, 592 per 100 million for diclofenac, 20 per 100 million for acetaminophen, and 25 per 100 million for metamizole. The estimates were largely influenced by the excess mortality associated with upper gastrointestinal complications. A relative risk estimate of 300 or more for the association of metamizole with agranulocytosis would have been necessary for the excess mortality of metamizole to be comparable to that of aspirin or diclofenac. Based on published epidemiologic evidence used to determine the excess mortality associated with short-term use of these four non-narcotic analgesics, the regulatory ranking of the drugs appears inappropriate. The excess mortality associated with short-term use of non-narcotic analgesics is presented in figure 1 below (Andrade SE et al. 1998).

Figure 1. The excess mortality associated with short-term use of non-narcotic analgesics /acetaminophen = paracetamol, dipyrone = metamizole/ (Andrade SE et al. 1998)



IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Dolamizol.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	• Blood dyscrasias (agranulocytosis, pancytopenia and aplastic anaemia) • Anaphylactic reactions including anaphylactic shock • Severe hypotensive reactions including vascular shock • Stevens-Johnson syndrome and toxic epidermal necrolysis • Drug-induced liver injury (DILI)
Important potential risks	• None
Missing information	• Breastfeeding

The MEB agreed that routine pharmacovigilance and risk minimisation activities are sufficient for the risks and areas of missing information. The MAH will provide additional educational material which consists of one Guide for prescribers (i.e. specialists in pain treatment who initiate metamizole in a hospital setting) and one Patient card (both for the risk of agranulocytosis and DILI). Other additional risk minimisation for the risk of agranulocytosis will be in place through a Controlled access program.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Algopyrin. No new clinical studies were conducted. The MAH provided a literature overview discussing the use of the active substance metamizole sodium monohydrate in the literature. Furthermore, the MAH demonstrated through a solubility and dissolution study that the drug product dissolves fully in medium and that the dissolution profile is similar to the reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English. The test consisted of: a pilot test with four participants, followed by three rounds with one round of four and two rounds of ten participants each. The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Dolamizol 250 mg and 500 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Algopyrin. Algopyrin is a well-known medicinal product with an established favourable efficacy and safety profile

The Board followed the advice of the assessors.

The MEB, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dolamizol with the reference product, and have therefore granted a marketing authorisation. Dolamizol was authorised in the Netherlands on 18 March 2021.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse
-	-	-	-	-	-

LITERATURE REFERENCES

Andrade SE, Martinez C, Walker AM. Comparative safety evaluation of non-narcotic analgesics. J Clin Epidemiol. 1998 Dec;51(12):1357-65.

Andrade S, Bartels DB, Lange R, Sandford L, Gurwitz J. Safety of metamizole: a systematic review of the literature. J Clin Pharm Ther. 2016 Oct;41(5):459-77.

Basak GW, Drozd-Sokołowska J, Wiktor-Jedrzejczak W. Update on the incidence of metamizole sodium-induced blood dyscrasias in Poland. J Int Med Res. 2010 Jul-Aug;38(4):1374-80.

Blaser LS, Tramonti A, Egger P, et al. Hematological safety of metamizole: retrospective analysis of WHO and Swiss spontaneous safety reports. Eur J Clin Pharmacol. 2015 Feb;71(2):209-17.

de Leeuw TG, Dirckx M, Gonzalez Candel A, et al. The use of dipyrone (metamizol) as an analgesic in children: what is the evidence? A review. Paediatr Anaesth. 2018 Mar;28(3):309.

Edwards, J.; Meseuger, F.; Faura, C. et al.: Single dose dipyrone for acute postoperative pain. (Intervention Review). The Cochrane Collaboration.

Gómez-Jiménez, J.; Franco-Patino, R.; Chargoy-Vera, J.; Olivares-Sosa, R.: Clinical efficacy of mild analgesics in pain following gynaecological or dental surgery: report on multicentre studies. Br. J. Clin. Pharmac. 10, 355S – 358S (1980)

Hamerschlak N, Maluf E, Biasi Cavalcanti A, et al. Incidence and risk factors for agranulocytosis in Latin American countries--the Latin Study: a multicenter study. Eur J Clin Pharmacol. 2008 Sep;64(9):921-9.

Hedenmalm K, Spigset O. Agranulocytosis and other blood dyscrasias associated with dipyrone (metamizole). Eur J Clin Pharmacol. 2002 Jul;58(4):265-74.

Hoffmann F, Meinecke P, Freitag MH, et al. Who gets dipyrone (metamizole) in Germany? Prescribing by age, sex and region. J Clin Pharm Ther. 2015 Jun;40(3):285-8.

Hoffmann F, Bantel C, Jobski K. Agranulocytosis attributed to metamizole: An analysis of spontaneous reports in EudraVigilance 1985-2017. Basic Clin Pharmacol Toxicol. 2019 Aug 26.

Huber M, Andersohn F, Sarganas G, et al. Metamizole-induced agranulocytosis revisited: results from the prospective Berlin Case-Control Surveillance Study. Eur J Clin Pharmacol. 2015 Feb;71(2):219-27.

Instituto Materno Infantil Professor Fernando Figueira (IMIP), Recife, Pernambuco, Brazil: Tepid sponging plus dipyrone versus alone for reducing body temperature in

febrile children. Sao Paulo Med. J.: 126 (2), 107 – 111 (2008)

Işık M, Kaya Z, Belen FB, et al. Life-threatening agranulocytosis, anemia, and plasmacytosis after dipyrone use for fever in a child. J Pediatr Hematol Oncol. 2014 Jan;36(1):e46-8.

Konijnenbelt-Peters J, van der Heijden C, Ekhart C, Bos J, et al. Metamizole (Dipyrone) as an Alternative Agent in Postoperative Analgesia in Patients with Contraindications for Nonsteroidal Anti-Inflammatory Drugs. Pain Pract. 2017 Mar;17(3):402-408.

Kötter T, da Costa BR, Fässler M, et al. Metamizole-associated adverse events: a systematic review and meta-analysis. PLoS One. 2015 Apr 13;10(4):e0122918.

Ladner, E.; Plattner, R.; Friesenecker, B. et al.: Nicht-Opioid-Analgetika – unersetzlich in der Tumorschmerz-therapie? Anästhesiol Intensivmed. Notfallmed. Schmerzther. 35, 677 – 684 (2000)

Maj S, Lis Y. The incidence of metamizole sodium-induced agranulocytosis in Poland. J Int Med Res. 2002 Sep-Oct;30(5):488-95

Martínez-Martín P.; Raffaelli E. Jr.; Titus F, et al.: Efficacy and safety of metamizol vs. acetylsalicylic acid in patients with moderate episodic tension-type headache: a randomized, double-blind, placebo- and active-controlled, multicentre study. Cephalalgia 21 (5), 604-10 (2001)

Planas, M. E.; Gay-Escoda, C. C.; Bagán, J. V. et al.: Oral metamizol (1 g and 2 g) versus ibuprofen and placebo in the treatment of lower third molar surgery pain: randomised double-blind multi-centre study. Eur. J. Clin. Pharmacol. 53, 405 – 409 (1998)

Ramacciotti A. S.; Soares B. G.; Atallah A. N.: Dipyrone for acute primary headaches. Cochrane Database Syst Rev. 18;(2), CD004842 (2007)

Rawal, N.; Allvin, R.; Amilon, A. et al.: Postoperative Analgesia at Home After Ambulatory Hand Surgery: A Controlled Comparison of Tramadol, Metamizol, and Paracetamol. Ambulatory Anesthesia 92, 347 – 351 (2001)

Reist L, Erlenwein J, Meissner W, et al. Dipyrone is the preferred nonopioid analgesic for the treatment of acute and chronic pain. A survey of clinical practice in German-speaking countries. Eur J Pain. 2018 Jul;22(6):1103-1112.

Rodríguez, M.; Barutell, C.; Rull, M. et al.: Efficacy and tolerance of oral dipyrone versus oral morphine for cancer pain. Eur. J. Cancer 30 A (5), 584 – 587 (1994)

Rohdewald, P.; Neddermann, E.: Dosisabhängigkeit der analgetischen Wirkung von Metamizol. Anaesthesist 37, 150 – 155 (1988)

San Bartolomé Mother-Child National Teaching Hospital, Lima, Peru: Antipyretic efficacy and tolerability of oral ibuprofen, oral dipyrone and intramuscular dipyrone in

children: a randomized controlled trial. Sao Paulo Med. J. 124 (3), 135 – 140 (2006)

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

Souza, J. F. D.; Lajolo, P. P.; Pincowsky, H.; de Giglio, A.: Adjunct dipyrone in association with oral morphine for cancer-related pain: the sooner the better. Support Care Cancer 15, 1319 – 1323 (2007)

Stammschulte T, Ludwig WD, Mühlbauer B, et al. Metamizole (dipyrone)-associated agranulocytosis. An analysis of German spontaneous reports 1990-2012. Eur J Clin Pharmacol. 2015 Sep;71(9):1129-38.

Tulunay F. C.; Ergün H.; Gülmez S. E.; et al.: The efficacy and safety of dipyrone (Novalgin) tablets in the treatment of acute migraine attacks: a double-blind, cross-over, randomized, placebo-controlled, multi-center study. Functional Neurology 19 (3), 197-202 (2004)

Varonos DD, Santamouris S, Karambali S. The incidence of dipyrone-induced agranulocytosis in Greece during 1975. J Int Med Res. 1979;7(6):564-8.

Wong, A.; Sibbald, A.; Ferrero, F. et al.: Antipyretic effects of dipyrone versus ibuprofen versus acetaminophen in children: results of a multinational, randomized, modified double-blind study. Clinical Pediatrics 40, 313 -324 (2001)

Yalcin, A.; Güllü, I. H.; Tekuzman, G. et al.: A comparison of two nonsteroidal anti-inflammatory drugs (diflunisal versus dipyrone) in the treatment of moderate to severe cancer pain. Am. J. Clin. Oncol. (CCT) 21 (2), 185 – 188 (1998)