CBG MEB

Public Assessment Report

Scientific discussion

Metamizol Will-Pharma 500 mg/ml solution for injection

(metamizole sodium monohydrate)

NL License RVG: 114598

Date: 16 May 2018

This module reflects the scientific discussion for the approval of Metamizol Will-Pharma 500 mg/ml solution for injection. The marketing authorisation was granted on 28 May 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

A list of literature references is given on page 15-16.

List of abbreviations

AA	4-aminoantipyrine
AAA	4-acetylaminoantipyrine
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CSF	Cerebrospinal Fluid
EDQM	European Directorate for the Quality of Medicines
ERA	Environmental Risk Assessment
FAA	4-formylaminoantipyrine
GST-P	Glutathione-S-Transferase - Placental
ICH	International Conference of Harmonisation
LD30	Half maximally Lethal Dose
MAA	4-methyl-amino-antipyrine
MAH	Marketing Authorisation Holder
NSAID	Non-steroidal Anti-inflammatory Drug
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
PSUR	Periodic Safety Update Report
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
SSRI	Selective Serotonin Reuptake Inhibitor
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 Metamizol Will-Pharma 500 mg/ml solution for injection from Will Pharma B.V.

The product is indicated in the short-term treatment of severe pain if other treatments are contraindicated, and in the treatment of high fever if other treatments have failed to provide relief or are contraindicated.

A comprehensive description of the indications and posology is given in the SmPC.

This application concerns a bibliographical application based on well-established medicinal use of metamizole solution for injection. This type of application does not require submission of the results of pre-clinical tests or clinical trials if it can be demonstrated that the active substance of the medicinal product has been in well-established medicinal use within the Community for at least 10 years, with recognised efficacy and an acceptable level of safety.

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

The active substance metamizole (synonym: dipyrone) is a non-steroidal anti-inflammatory drug (NSAID). It is a water soluble pyrazolone derivative available in oral, rectal and injectable forms. The pyrazolone-derivative group of medicinal agents is often classified as aspirin-like or peripherally acting, which implies that they interfere with prostaglandin synthesis. Since its introduction in 1922 it has been recognised as an effective analgesic, antipyretic and antispasmodic drug. Compared with other NSAIDs, metamizole has a small anti-inflammatory activity. Metamizole was registered in the Netherlands in 1989 by Sanofi-Aventis Netherlands B.V. under the brand name Novalgin 1 g/2 ml solution for injection (NL License RVG 04069). This product is no longer registered.

II. QUALITY ASPECTS

II.1 Introduction

Metamizol Will-Pharma 500 mg/ml is a clear, almost colourless to brownish-yellow coloured solution, practically free from particles, with pH 6.0-8.0 Each ml of solution contains 500 mg metamizole sodium monohydrate.

It is packed in 2 ml and 5 ml brown (amber) type I hydrolytic glass ampoules.

The excipients are: hydrochloric acid (for pH adjustment) and water for injection.

II.2 Drug Substance

The active substance is metamizole sodium monohydrate, a well known drug substance described in the European Pharmacopoeia (Ph.Eur.). It is a white to almost white, crystalline powder which is very soluble in water. In view of its water solubility, physical characteristics of metamizole sodium such as particle size distribution, bulk density or flow properties are not crucial for this liquid dosage form.

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 Ph.Eur.

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

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur., with additional requirements for residual solvents, microbiological requirements and bacterial endotoxins. The limits for impurities are adequate in view of the maximum daily dose of 3 g. Batch analytical data demonstrating compliance with the specification have been provided for four batches.

Stability of drug substance
The active substance is stable for 5 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
Adequate data has been provided on the drug substance, excipients, formulation development, manufacturing process development, sterilization method and container closure system. Terminal sterilization for the product was chosen due to the characteristics of drug substance. The brown ampoule is meant as protection measure from light, although this is a disadvantage as the parenteral solution cannot be properly inspected on particulate matter due to this brown glass.
The pharmaceutical development has been sufficiently explained.

Manufacturing process
Preparation and filtration of the solution for injection (with in-process controls on pH and osmolality) and filling of ampoules (with in-process controls on extractable volume) are considered as critical steps.
The manufacturing process has been adequately described. Sterilisation of the filled ampoules is performed by a pharmacopoeial method (steam sterilizer). No significant decomposition of the drug substance has been observed. Filling and sealing of the ampoules must be performed under aseptic conditions. The proposed in-process controls and their acceptance criteria are considered adequate. Two batches of metamizole 500 mg/ml (2 ml) have been validated regarding the various holding times. For metamizole 500 mg/ml in 5 ml ampoules similar validation has been initiated.

Control of excipients
The excipients meet the requirements of the Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The specification is adequate and includes tests for description, extractable volume, clarity and degree of opalescence, degree of coloration, particulate contamination, pH, identification of metamizole sodium, assay of metamizole sodium monohydrate, related substances, sterility and bacterial endotoxins. The analytical methods have been adequately described and validated.
Batch analysis results are provided for 3 batches of 2 ml ampoules and 3 batches of 5 ml ampoules. All results were in accordance with the set release specifications.

Stability of drug product
The MAH has provided stability data on 3 stability batches per ampoule volume (2 ml and 5 ml) performed with old specifications for related substances and without test on particulate contamination, tested for 60 months at 25°C/60% RH and for 6 months at 40°C/75% RH.
Results of newer studies were provided on 2 stability batches for 2 ml ampoules and 1 stability batch for 5 ml ampoules, tested for 48 months at 25°C/60% RH including a test on particulate contamination. All results were in accordance with the set requirements.
Additional studies for 3 recent batches have been performed. All results from the additional stability studies were in accordance with the set shelf-life specifications. The drug substance is sensitive to light.
The granted shelf life is 4 years if stored in 2 ml or 5 ml glass type 1 ampoules not above 25°C. Additional storage conditions are ‘Store in the original package in order to protect from light. Do not store in the freezer’.

Specific measures for 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 Metamizol Will-Pharma 500 mg/ml solution for injection has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.
No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

In preclinical studies metamizole was shown to be a potent analgesic and antipyretic drug with very little anti-inflammatory effect at therapeutic doses in man and in behavioural experiments on animals.
The mode and site of action of metamizole (dipyrone) still remain partially unresolved. Literature review has suggested a diversity of mechanisms of action that may have been modulated by the site of action, the type of administration and the dosages in use or the agents in use to prove the mechanisms (i.e. block the effects of metamizole). The key sites/systems of action for which the literature has been reviewed by the MAH are:

- controversial data on site of analgesic action, peripheral vs. central
- review of mechanisms similar in use of other NSAIDs
- mechanisms involving prostaglandin E2-induced effects
- effects on cyclooxygenase variants
- effects on ion channels
- site of action at the periaqueductal gray matter
- the involvement of opioidergic systems.

Other effects that have been reported for metamizole include:

- dose-dependent reduction of the frequency of ureter contractions (*in vitro* sheep ureters)
- dose-dependent delay in gastric emptying (*in vivo* in rats)
- inhibition of arachidonic acid induced platelet aggregation *in vitro* indicative of a relatively strong prohaemorrhagic potential (when compared to other NSAIDs)
- spasmolytic properties by either local or iv administration (relaxation on several types of vascular smooth muscles)
- anticonvulsant action (*in vivo*)
- inhibition of G6PD activity (*in vitro* and *in vivo*).

One study found that metamizole administered repeatedly to mice demonstrated a weaker antinociceptive effect than after a single dose.

Drug-drug interaction studies
The antinociception induced by the intraperitoneal co-administration in mice of combinations of metamizole and paracetamol revealed synergistic antinociception of the combination.
Co-administration of metamizole and morphine was shown to have beneficial acute and chronic antinociceptive effects in drug-naive rats.
The SSRI sertraline after single dose increased the antinociceptive effect of metamizol.
Metamizole did not alter the effects of morphine on the inhibition of gastrointestinal transit, but was able to antagonise the antitransit effects of tramadol.
One study indicated that mianserin in a single dose or administered for 14 days together with metamizole increased the antinociceptive effect of metamizol.
The single dose of oxcarbazepine administered with metamizole did not affect the antinociceptive action of metamizole while repeated (10 days) use of oxcarbazepine together with metamizole significantly prolonged the latency of nociceptive reaction in mice.

III.2 Pharmacokinetics

Pharmacokinetic data for metamizole in animals is limited to some species. More data is available for humans.

Absorption
Metamizole (dipyrone) is considered a prodrug which is metabolized in the intestinal tract to the active metabolite, 4-methyl-amino-antipyrine (MAA), which is then metabolized in the liver to a second active metabolite 4-aminoantipyrine (AA). Dipyrone is also rapidly undetectable in plasma after iv doses. None of the metabolites of dipyrone are extensively bound to plasma proteins.
The biological half-life is 2.7 hours in rat and 5.2 hours in dog.

Distribution
None of the metabolites of metamizole are extensively bound to plasma proteins. Most of a dose is excreted in the urine as metabolites. Dipyrone metabolites are also distributed into breast milk.

Metabolism
Metamizole is a prodrug which, at room temperature and in an atmosphere with oxygen, is spontaneously, non-enzymatically converted to MAA. *In vitro*, metamizole is degraded with a half-life of 16 minutes. The identity of the specific isoform(s) involved in biotransformation is not completely understood, the findings in several preliminary studies have suggested that CYP3A4 is probably the major enzyme mediating the N-demethylation of MAA to AA.

Excretion
Most of a dose is excreted in the urine as metabolites. The elimination half-life of metamizole in the dog is reported to be 4-5 hours.

Factors affecting pharmacokinetics in humans (human data): While renal clearance of all 4 metabolites decreased in linear relationship to creatinine clearance, apparent clearance of MAA and AA remained unaltered in patients with different degrees of renal impairment. Significant differences were found between the cirrhotic and healthy individuals for t_{max}, $t_{1/2}$ and apparent clearance.

Pharmacokinetic drug interactions
Pharmacokinetic drug interactions by using the same metabolic pathways cannot be excluded (CYP3A4 is major metabolising enzyme). As metamizole induces delayed gastric emptying, potentially any medication with expected absorption within the intestines may have kinetic interactions with metamizole treatment.

III.3 Toxicology

Metamizole was found to be cytotoxic to a variety of plant (onion) and animal (fish) cells. LD30 following iv administration was 2389 and 1236 mg/kg in rats and mice respectively.
A high dose of dipyrone (1000 mg/kg) induced slight erosions in rat gastric mucosa which are probably related to the changes induced in glutathione metabolism (inhibition of glutathione peroxidase activity).
Dipyrone was well tolerated in rats in a 4-week toxicity study with doses up to 450 mg/kg/day iv, and chronic toxicity study up to 900 mg/kg together with food. The only abnormalities were increased numbers of Heinz bodies and reticulocytes. In the chronic study slight signs of siderosis occurred in the Kupffer cells of the liver and in the spleen, at the high dose level.
In dogs also the appearance of Heinz bodies in the red blood cells was seen (at 450 mg/kg in a 4-week toxicity study and at ≥ 100 mg/kg in a 6-month study). Furthermore salivation and occasionally vomiting, and reduced weight gain was seen. Signs of haemosiderosis were seen in several organs in the 6-month study. Also some haematological effects were seen (reduced haemoglobin, red blood cells and leucocytes, increased reticulocytes).

Agranulocytosis
Pyrazolones, mainly aminopyrine and dipyrone, have been associated with leukopenia or agranulocytosis. The underlying mechanism of this process in the case of aminopyrine has been identified to be the occurrence of aminopyrine-binding antibodies in the blood of affected patients.
In rats no statistically significant changes occurred in the blood picture with respect to red cell, white cell, and differential counts when varying amounts of dipyrone were administered orally.

Only limited data on genotoxic potential is available and no standard carcinogenicity studies have been performed. However data indicate that: (i) dipyrone enhanced liver carcinogenesis of rats initiated with diethylnitrosamine, but did not act as an initiator or a complete carcinogen; (ii) dipyrone administered for 25 or 72 weeks increased GST-P+ preneoplastic lesions; (iii) both forms of dipyrone (A and B which had almost the same purity), exerted almost the same enhancing effect in a medium-term bioassay system for liver carcinogenesis; (iv) dipyrone was weakly mutagenic in the Ames mutation test (v); dipyrone has no transplacental carcinogenic effect.

Data on reproductive toxicity are very limited. In sheep metamizole was found to decrease sperm volume, increased hyaluronidase activity of semen and increased spermatozoa motilities. A block at the G1 and S subphases or G2 subphase was seen in rat placental cells in early or mid stages of pregnancy respectively. No effects were seen closer to term.

The genotoxic potential of metamizole has been assessed by the European Medicine Agency (EMA). As stated in the "Metamizole Summary report", several *in vitro* assays for gene mutation have been carried out using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, and Escherichia coli WP2uvrA. All the studies which were adequately described gave negative results. Positive results were claimed in published *in vitro* cytogenetics assays in human lymphocytes and in sister chromatid exchange assays in Chinese hamster cells but little or no information was provided concerning the test methods or the purity of the substances tested and full details of the results were not provided; the results were therefore difficult to interpret (EMA, 2003). Oral doses of 0, 25, 200 or 1600 mg/kg body weigh were administered to NMRI mice in an *in vivo* micronucleus test; a negative result was obtained but there was no positive control group and no evidence of bone marrow toxicity. A second *in vivo* micronucleus test was reported in the literature but gave no details beyond a statement that metamizole was positive. Published studies were also reported on the mutagenic potential of nitrosation products of metamizole in the *in vitro* assay for gene mutation in bacteria (Ames test); two studies claimed positive results but the third, which was the most adequately reported, claimed negative results (Kramer, 1980; CCRIS Dipyrone, 1995; Giri and Mukhopadhyay, 1998).
In well-conducted mutagenicity assays (*in vitro* gene mutations and *in vivo* micronucleus test), which were carried out in compliance with Good Laboratory Practice and relevant Organisation for Economic Co-operation and Development (OECD) guidelines, it was concluded that metamizole was not genotoxic (EMA, 2003).

III.4 Ecotoxicity/environmental risk assessment (ERA)

The product is likely to replace existing marketed metamizole containing products. The approval of this product will not result in an increase in the total quantity of metamizole released into the environment. Further environmental risk assessment is therefore not considered necessary.

III.5 Discussion on the non-clinical aspects

Pharmacodynamic, pharmacokinetic and toxicological properties of the active substance are well known. An overview based on literature review is, thus, appropriate. The MAH submitted a Non-clinical Overview. This overview is adequate.
The analgesic and antipyretic effects of metamizole are well documented. While the mode of action appears to have been the subject of many studies, clear conclusions on the mode of actions cannot be drawn except that multiple pathways appear to be involved in its pharmacodynamic action.
The fact that metamizole inhibits G6PD activity indicates that care should be taken when using metamizole in patients with severe G6DP deficiency.
Although some positive results are reported in the literature, overall it can be concluded that metamizole is not genotoxic.
Metamizole has been banned in multiple countries, mainly because of a risk of agranulocytosis and other adverse haematological effects. It is noted that no signs of haematological effects were noted in rats, while slight effects have been observed in dogs. However, considering the human data and the fact that a mechanism has already been identified, it is agreed that no further animal studies are needed to characterise the risks of haematological adverse effects.

IV. CLINICAL ASPECTS

IV.1 Introduction

This application concerns a well-established use application, based on article Article 10(a) for metamizole solution for injection. No clinical studies have been submitted to support this application.
The MAH submitted a Clinical Overview, based on published literature (115 references, dated between 1966 and 2010).

IV.2 Pharmacokinetics

Metamizol Will-Pharma is an aqueous solution containing also hydrochloric acid (3.6% of solution) for pH adjustment. Hydrochloric acid for pH adjustment is not considered to have an influence on physiochemical properties of metamizole.
The absence of a bioequivalence study is considered acceptable because it concerns an aqueous solution for injection with the same concentration of active substance, hence with comparable bioavailability. Bridging between the formulations used in the literature and the proposed formulation is justified.

Bioavailability
Metamizole is a parent drug, and is rapidly hydrolysed to 4-methyl-amino-antipyrine (MAA). In the review article by Levy et al. (1995), the absorption of MAA via different administration routes (i.e. the mouth, the rectum and parenteral) was summarized based on studies in healthy volunteers. The bioavailability of MAA was 85% for the tablets, 89% for the drops, 54% for the suppositories and 87% for the intramuscular (im) injection. As the bioavailability of MAA for the tablets and the IM injection were comparable, the maximum concentration (C_{max}) was not expected to be markedly different. With a single im injection of metamizole, the C_{max} of MAA was 11.4 mg/l (t_{max}=1.7 hours) in 12 healthy volunteers (Levy et al. 1995).

The linearity of C_{max} of MAA along with dose has been identified with a single-dose study using metamizole tablets with 0.75, 1.5 and 3 g doses (Vlahov et al., 1990).

Distribution
According to the publication by Zylber-Katz et al. (1985), the mean plasma protein binding of MAA was 57.6% (the range of 27 - 78%) in 20 healthy volunteers after oral administration of 1000 mg metamizole.

Levy et al. (1995) report the mean volume of distribution of MAA as 33.5 l in healthy volunteers after intravenous administration of metamizole.

In a study with 8 lactating women following a single oral dose of metamizole 1000 mg, MAA was detected in human breast milk with the mean milk-to-plasma concentration ratio of 1.37 ± 0.28 (Zylber-Katz et al., 1986). The disposition pattern of MAA in breast milk was studied in two lactating women (a slow and a fast acetylator). MAA was undetectable after 48 hours.

MAA can pass the blood-brain barrier. The concentration of MAA in cerebrospinal fluid (CSF) was measured after an oral single dose of metamizole 1000 mg in 28 patients undergoing diagnostic lumbar puncture (Cohen et al., 1998). Mean CSF/plasma ratios were 0.4 (for samples taken at 0.5-2 h) and 0.83 (for samples taken at 4-12 h) for MAA. Significant correlation was found between plasma and CSF concentration for MAA.

Metabolism and elimination
After intravenous administration, metamizole is hydrolysed to MAA in the intestine. MAA is then metabolized by demethylation to AA and by oxidation to 4-formylaminoantipyrine (FAA). AA is further metabolized to 4-acetylaminoantipyrine (AAA). AA, FAA and AAA are the major inactive metabolites of metamizole. Some unchanged metamizole is excreted into the kidneys and converted to MAA here (Levy et al., 1995).

The secondary metabolism of metamizole is highly variable resulting from the activity of the hepatic polymorphic N-acetyl-transferase system. The significant difference was found for AA half-life of 8.1

hours for slow and 3.7 hours for rapid acetylators in a study with 23 volunteers (Levy et al., 1984). In MAA, the pharmacokinetics did not differ between 9 slow and 3 rapid acetylators after oral administration (Zylber-Katz, 1992).

Metamizole is mainly eliminated via kidneys. After oral or intravenous administration, more than 90% of the administered radioactivity is recovered in the urine and less than 10% was recovered in the faeces (Levy et al. 1995). The major 4 metabolites of metamizole account for about 60% of the administered dose.

In the review article by Levy et al. (1995), the elimination half-life ($t_{1/2}$) of MAA was 2.8-3.2 hours after parenteral administration, which was comparable with oral administration (2.5-3.7 hours). After parenteral administration, the half-lives of AA, AAA and FAA were 6.2-8.6 hours, 11.1-12.4 hours and 9.7-13.1 hours, respectively. The apparent total body clearance (CL/F) of MAA was 150-168 ml/min and the renal clearance was 4-28 ml/min after parenteral administration.

Pharmacokinetics in special populations
The study done by Zylber-Katz (1989) showed a mean prolonged MAA elimination in 9 elderly ($t_{1/2}$=4.5 hours) compared with 12 young individuals ($t_{1/2}$=2.6 hours).

No gender difference in pharmacokinetics of MAA was seen in a single-dose study (Levy et al., 1984). There was no study investigating gender difference after multiple-dose administration of metamizole.

In the review by Levy et al. (1995), total body clearance of MAA and AA were not changed in a study where 24 patients with impaired renal function were administrated a 1000 mg oral dose. Lower clearance and prolonged $t_{1/2}$ was observed in 6 patients with chronic renal failure after intravenous administration. In patients with liver disease, the elimination phase of MAA was prolonged as an increase of $t_{1/2}$ and a decrease of apparent total clearance.

With regard to the paediatric population, it has only been mentioned that children aged 1-11 years have a shorter elimination half-life than adults (Levy et al., 1995). The MAH did not identify further references regarding paediatric pharmacokinetics in the literature.

Pharmacokinetic drug interaction
The review paper by Levy et al. (1995) is also referred to regarding drug interactions. It is stated that the pharmacokinetics of alcohol (1 g/kg) were not altered by administration with metamizole (1000 mg). There was no interaction between glibenclamide and metamizole, and metamizole (1000 mg 3 times daily for 3 days) did not affect the diuretic effect of flurozemide (20 mg injection).

Short-term administration of metamizole has been shown to reduce the blood concentration of cyclosporine A by Caraco et al (1999).

IV.3 Clinical efficacy

The MAH initially applied for the following indications:
'The treatment of severe or persistent pain that does not respond to other forms of treatment:
- actue renal colic
- headache
- postoperative pain
- other acute pain symptoms.

The treatment of severe or persistent fever that does not respond to other forms of treatment.'

Metamizole solution for injection has been registered in the Netherlands as Novalgin for the indication 'short-term treatment of severe pain if other treatments are contraindicated, and in the treatment of high fever if other treatments have failed to provide relief or are contraindicated.' Following comments of the MEB, the proposed indication for Metamizol Will-Pharma was changed to the same indication as Novalgin.

The MAH submitted a clinical overview containing 33 publications to support the efficacy of metamizole.

The efficacy of metamizole (administered intravenously or intramuscularly) in the treatment of pain in patients with an acute renal colic is demonstrated in 8 publications including randomized, double-blind, controlled comparisons with other analgesics (e.g. diclofenac) and placebo. The efficacy of metamizole has been demonstrated in over 1.000 patients.

The efficacy of metamizole (administered intravenously or orally) in the treatment of pain in patients with headache (including headache in migraine patients) is demonstrated in 5 publications including a meta-analysis (published in 2007) on 4 trials involving a total of 636 adult subjects. In addition 4 publications are discussed. The efficacy of metamizole has been demonstrated in over 1.000 patients.

The efficacy of metamizole (administered intravenously, intramuscularly or orally) in the treatment of postoperative pain is demonstrated in 18 publications including a meta-analysis (published in 2010) on 15 trials involving a total of 433 adult subjects treated with metamizole. In addition the efficacy of metamizole is compared with paracetamol in 6 publications, with parecoxib in 3 publications, with lornoxicam in 3 publications and with ketorolac in 2 publications. Six publications pertaining to the relief of early postoperative pain by treatment including metamizole are discussed.

The efficacy of metamizole in the treatment of other pain symptoms (painful knee trauma, biliary pain and pain due to acute pancreatitis) is discussed in 3 publications. These studies are considered supportive evidence as they were not randomized and blinded.

The efficacy of metamizole in the treatment of severe or persistent fever unresponsive to other treatments the efficacy of metamizole (administered intravenously or intramuscularly) is demonstrated in 4 publications including randomized, double-blind, controlled comparisons with other analgesics. In total 556 patients have been studied. Thus the efficacy of metamizole has been demonstrated in a substantial number of patients.

IV.4 Clinical safety

The MAH concludes that metamizole is a known analgesic drug with minor toxic effects associated with its administration. However, the potential to induce agranulocytosis seems to be associated with genetic characteristics of the population studied, as in German and Spanish patients the occurrence of agranulocytosis is much lower than in other countries where metamizole is widely used (i.e. Central and Eastern Europe, Asia). Data collected from 8 population groups in Europe and Israel by the International Agranulocytosis and Aplastic Anemia Study revealed that there was a significant regional variability in the rate-ratio estimate for agranulocytosis and metamizole (0.9 in Budapest to 33.3 in Barcelona). Although a large relative increase in risk between agranulocytosis and use of metamizole was found, the incidence was less than some previous reports had suggested. Blood dyscrasias such as agranulocytosis and granulocytopenia have continued to be reported where metamizole remains available.

Safety of metamizole remains subject of debate, i.e. agranulocytosis and anaphylactic shock. These risks have been reason to withdraw oral metamizol medicinal products in several other European countries and the USA. Basically agranulocytosis and anaphylactic shock appears idiosyncratic.
According to Schönhofer et al. (2003) the frequency of serious adverse drug reactions, not lack of efficacy, makes dipyrone unacceptable for therapeutic use. Their conclusion was based on an on-going discussion about the incidence of metamizole-induced agranulocytosis ranging from 1 in 20,000 to 1 in 7 million. In addition it was suggested that even the incidence of 1 in 20,000 is an underestimation as this number is based on the annual data of a spontaneous reporting system in the eighties. Since at that time only about 5% of all serious events reached the spontaneous reporting systems, the real incidence should be 1 in 1,000 users per year. In the clinical overview published data on the incidence of metamizole-induced agranulocytosis is summarised.

The MAH indicates that anaphylactic shock which has resulted in fatalities has been reported with metamizole (incidence: 1 in 5000 administrations) (DRUGDEX® Evaluations; Ribera et al. 1981). Non-fatal anaphylactic events were also reported (Eckle et al. 2005, Janke et al. 2003).

IV.5 Discussion on the clinical aspects

Based on the provided literature overview, the MEB formulated two major objections: one with regard to the posology for children, and one related to the benefit/risk balance due to unclear incidence of agranulocytosis and anaphylactic shock when using metamizole.

Paediatric labelling
Novalgin is indicated in children from body weight >18 kg. The MAH submitted studies from the literature to justify the proposed dose in paediatric patients with a minimum body weight of 7 kg, and minimum age of 6 months. The mean body weight of children aged 6 months in the Netherlands is about 7 kg.
This was based on three articles where a minimum age of 6 months was used for inclusion of patients: Yilmaz et al. (2003), Wong et al. (2001) and Prado et al. (2006). Even though only Yilmaz et al. described the mean age of the study group (36 months) and no pharmacokinetic data were available, the total number of studied paediatric patients was high (in total 855 patients; N=225, N=555, N=75, respectively) and no serious adverse events were reported. The exact number of children <18 kg that were included, equivalent to children younger than 4 year old, is unknown. However, as the studies were large-scaled, the minimal inclusion age was 6 months, and the data did not indicate an age-dependency regarding safety, this is accepted. However, Yilmaz et al. state that "in view of its known side effects and the problem associated with intramuscular administration in children, the preference for orally administered nimesulide or ibuprofen over dipyrone in the setting of the emergency department seems more logical provided that the child accepts oral therapy." Furthermore, three studies used 15 mg/kg for treatment without major safety issues, and one study used 10 mg/kg. Therefore, the proposed dosage of 10-12 mg/kg body weight in children is considered sufficiently justified. A statement on the lack of pharmacokinetic data for infants/children <6 months has been added to section 5.2 of the SmPC.

Safety - risk of agranulocytosis and anaphylactic shock
Additional data regarding the risk of agranulocytosis and anaphylactic shock was required. With regard to the risk of agranulocytosis the MAH updated the Clinical Overview. Edwards et al. (2010) systematically reviewed literature between 1999-2010 and did not find new evidence regarding the incidence or risk of agranulocytosis in patients using metamizole. Basak et al. (2010) analysed cases of agranulocytosis and aplastic anaemia in 24 out of 25 centres that provided haematology care for the entire adult population in Poland. They found 0.7 cases of agranulocytosis per million adults per year, lower than a previous study from Poland (Maj et al., 2004) and several international studies (Kaufman et al, 2006). Basak and colleagues concluded that drug-induced blood duscrasias with the use of metamizole are rare and that the drug may be considered relatively safe. Overall, there remains a huge variance in incidence of this severe adverse event between studies.
Also with regard to the risk of anaphylactic shock the MAH updated the Clinical Overview. No recent literature references (published after 2010) have been found.
Incidences reported differ from fatal anaphylactic shock in 1 out of 5000 administrations (Ribera et al. 1981) to an excess mortality estimate of 0.22 per 100 million (Van der Klauw et al. 1998). The incidence of non-fatal anaphylactic events differed from 3.7 per million annually (Van der Klauw et al. 1993) to 7 per 100.000 exposed patients (The International Collaborative Study of Severe Anaphylaxis, 2003).

Pharmacovigilance
Findings in relevant PSURs support a very rare incidence of agranulocytosis and anaphylactic shock in using metamizole solution for injection.

Clinical context
The MEB gathered further information about the clinical context and controllability of metamizole in the Netherlands in order to assess whether the clinical benefits outweigh the risks. In the guideline on postoperative pain of the Dutch Society of Anaesthesiology (*Richtlijn postoperatieve pijn. Nederlandse Vereniging voor Anesthesiologie (NVA) 2012*) dipyrone is included as an effective analgesic for mild to moderate postoperative pain. It is indicated that side-effects are more rare than for other NSAIDs. Furthermore dipyrone is recommended as a good alternative for patients with a relative or absolute contraindication for NSAIDs.

Benefit-risk balance

The MAH has sufficiently justified the proposed dose of 10-12 mg/kg body weight in paediatric patients with a minimum body weight of 7 kg, and minimum age of 6 months.

With regard to efficacy, metamizole has a different mode of action than other NSAIDs. It is effective for the treatment of pain and high fever, and efficacy is not at stake. The benefit/risk balance discussion is focused on the safety, i.e. the risk on agranulocytosis and anaphylactic shock.
With regard to safety, the risk on metamizole-induced agranulocytosis and anaphylactic shock has also to be placed in the risk on adverse events, induced by alternative medicines. The well-established NSAIDs and paracetamol are all at risk for (rare) adverse events. In addition, the findings from pharmacovigilance point of view support a very rare incidence of agranulocytosis and anaphylactic shock. Taking all this into consideration, it can be concluded that the effectiveness and different mode of action of metamizole injection outweighs the risks of agranulocytosis and anaphylactic shock. Furthermore, consulted experts are considered positive about metamizole solution for injection and included the drug in the guideline 'post-operative pain' of the NVA in 2012.

The rare risk on a serious adverse event induced by metamizole, have to be outweighed against the benefits; effective reduction of pain and effective reduction of the temperature. As metamizole has a different mode of action, it may be an alternative for patients who have contraindications or are irresponsive to alterative treatments. In patients suffering from severe pain or high fever, not responding or intolerant to other drugs, the benefit/risk is therefore considered positive.

IV.6 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 Metamizol Will-Pharma 500 mg/ml solution for injection.

- Summary table of safety concerns as approved in RMP

Important identified risks	• agranulocytosis and other blood disorders • anaphylactic/anaphylactoid reactions (including anaphylactic shock) • cardiovascular reactions (including hypotensive reactions) • severe skin reactions (including toxic epidermal necrolysis and pemphigus vulgaris) • renal toxicity and renal failure • foetal and neonatal toxicity
Important potential risks	• gastrointestinal haemorrhage
Missing information	• fertile women

The MEB agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information. The MAH committed to re-evaluate and discuss the issue of (paediatric) off-label use at next PSUR as this risk cannot be excluded based on the available data.

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 test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
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

Metamizol Will-Pharma 500 mg/ml solution for injection has a proven chemical-pharmaceutical quality. The use of the active substance in short-term treatment of severe pain and in the treatment of high fever is considered well-established. Adequate non-clinical and clinical literature data have been provided.

In the Board meetings of 30 January 2014, 17 September 2014 and 2 October 2014 the application was discussed. The comments of the Board have been adequately addressed by the MAH. The MAH has sufficiently shown that Metamizol Will-Pharma injection has a favourable efficacy and safety profile, and that the risks of agranulocytosis and anaphylactic shock can be considered rare.

The MEB considered that well-established use has been demonstrated for this medicinal product and has therefore granted a marketing authorisation. Metamizol Will-Pharma 500 mg/ml solution for injection was authorised in the Netherlands on 28 May 2015.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ Non-approval	Assessment report attached
Addition of a new testing site; addition of a manufacturer responsible for batch release not including batch control/testing.	IA/G	24-6-2015	4-8-2015	Approval	N
Submission of a new or updated Ph.Eur. certificate of suitability. New certificate from a new manufacturer.	IA/G	23-11-2016	1-12-2016	Approval	N

Literature references

Basak GW, Drozd-Sokołowska J, Wiktor-Jedrzejczak W (2010) Update on the incidence of metamizole sodium-induced blood dyscrasias in Poland. J Int Med Res 38: 1374-1380.

Caraco Y, Zylber-Katz E, Fridlander M, Admon D, Levy M. The effect of short-term dipyrone administration on cyclosporin pharmacokinetics. Eur J Clin Pharmacol. 1999; 55(6):475-478.

Chemical Carcinogenesis Research Information System (CCRIS) Dipyrone (1995); http://toxnet.nlm.nih.gov

Cohen O, Zylber-Katz E, Caraco Y, Granit L, Levy M. Cerebrospinal fluid and plasma concentrations of dipyrone metabolites after a single oral dose of dipyrone. Eur J Clin Pharmacol. 1998; 54(7):549-553.

Discombe G. Agranulocytosis caused by amidopyrine, an avoidable cause of death. Br. Med. J. 1952; 1 (4771): 1270-3.

DRUGDEX® Editorial staff. Dipyrone (DRUGDEX® Evaluations). In: Klasco RK, editor. DRUGDEX® System. Greenwood Village, Colorado: Thomson Micromedex, 2010.

Eckle T, Ghanayim N, Trick M, Unertl K, Eltzschig HK. Intraoperative metamizol as cause for acute anaphylactic collapse. Eur J Anaesthesiol. 2005; 22(10):810-812.

Edwards J, Meseguer F, Faura C, Moore RA, McQuay HJ, Derry S. Single dose dipyrone for acute postoperative pain. Cochrane Database Syst Rev. 2010 Sep 8;(9):CD003227. doi: 10.1002/14651858.CD003227.pub2.

Giri A.K., Mukhopadhyay A. (1998) Mutagenicity assay in Salmonella and in vivo sister chromatid exchange in bone marrow cells of mice for four pyrazolone derivatives. Mutat. Res., 420, 15-25.

Hugely CM. agranulocytosis induced by dipyrone, a hazardous antipyretic and analgesic JAMA 1964; 189: 938-41.

Janke C, Schmeck J, Passani D, Dodidou P, Stuck B, Kerger H. [Anaphylactic cardiocirculatory failure after intraoperative application of dipyrone]. Anaesthesist. 2003; 52(4):321-325.

Kaufman DW, Kelly JP, Issaragrisil S, et al: Relative incidence of agranulocytosis and aplastic anemia. Am J Hematol 2006; 81: 65 – 67.

Kramer M. Chronic toxicity of pyrazolones: the problem of nitrosation. Br J ClinPharmacol. 1980 Oct; 10 Suppl 2:313S-317S. Review. PubMed PMID: 7002188; PubMed Central PMCID: PMC1430166.

Levy M, Flusser D, Zylber-Katz E, Granit L. Plasma kinetics of dipyrone metabolites in rapid and slow acetylators. Eur J Clin Pharmacol. 1984; 27(4):453-458.

Levy M, Zylber-Katz E, Rosenkranz B. Clinical pharmacokinetics of dipyrone and its metabolites. Clin Pharmacokinet. 1995; 28(3):216-234.

Maissan IM, Klimek M, Huygen FJPM: Metamizol wèl geschikt bij acute pijn. Med Contact. 2012; 67: 723-5.

Maj S, Centkowski P: A prospective study of the incidence of agranulocytosis and aplastic anemia associated with the oral use of metamizole sodium in Poland. Med Sci Monit 2004; 10: PI93 – PI95.

Prado J, Daza R, Chumbes O, Loayza I, Huicho L. Antipyretic efficacy and tolerability of oral ibuprofen, oral dipyrone and intramuscular dipyrone in children: a randomized controlled trial. Sao Paulo Med J. 2006;124(3):135-40

Ribera A, Monasterio J, Acebedo G, Triginer J, Martin C. Dipyrone-induced immune haemolytic anaemia. Vox Sang. 1981; 41(1):32-35.

Schönhöfer P, Offerhaus L, Herxheimer A. Dipyrone and agranulocytosis: What is the risk? Lancet 2003;361: 12094

Van der Klauw MM, Stricker BH, Herings RM, Cost WS, Valkenburg HA, Wilson JH. A population based case-cohort study of drug-induced anaphylaxis. Br J Clin Pharmacol. 1993 Apr;35(4):400-8.

Van der Klauw MM, Wilson JH, Stricker BH. Drug-associated agranulocytosis: 20 years of reporting in The Netherlands (1974-1994). Am J Hematol. 1998; 57(3):206-211.

Vlahov V, Badian M, Verho M, Bacracheva N. Pharmacokinetics of metamizol metabolites in healthy subjects after a single oral dose of metamizol sodium. Eur J Clin Pharmacol. 1990; 38(1):61-65.

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

Yilmaz HL, Alparslan N, Yildizdas D, Bayram I, Alhan E. Intramuscular Dipyrone versus Oral Ibuprofen or Nimesulide for Reduction of Fever in the Outpatient Setting. Clin Drug Investig. 2003; 23(8):519-526

Zylber-Katz E, Granit L, Levy M. Plasma protein binding of dipyrone metabolites in man. Eur J Clin Pharmacol. 1985; 29(1):67-71.

Zylber-Katz E, Linder N, Granit L, Levy M. Excretion of dipyrone metabolites in human breast milk. Eur J Clin Pharmacol. 1986; 30(3):359-361.

Zylber-Katz E, Granit L, Stessman J, Levy M. Effect of age on the pharmacokinetics of dipyrone. Eur J Clin Pharmacol. 1989; 36(5):513-516.

Zylber-Katz E, Granit L, Levy M. Formation and excretion of dipyrone metabolites in man. Eur J Clin Pharmacol. 1992; 42(2):187-191.