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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

## Assessment report

Referral under Article 31 of Directive 2001/83/EC

metamizole-containing medicinal products

INN: metamizole sodium

Procedure number: EMEA/H/A-31/1469

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# 1. Information on the procedure

Metamizole (or dipyrone) is a non-addictive analgesic with analgesic, antipyretic and spasmolytic effects. It is indicated for severe acute and chronic pain and also for fever which is not responding to other treatments. It is authorised in several member states in European Union (EU).

In the frame of a Non Urgent Information (NUI) request, the maximum daily dose and contraindications in pregnancy and breastfeeding were investigated for all metamizole-containing products authorised in European Union (EU). As a result of this investigation, it was observed that the maximum daily dose of metamizole reflected in the Product Information of the different medicinal products varies from 1,5 g to 6 g. With regards to contraindication in pregnancy and breastfeeding, discrepancies were also noted. The active substance is contraindicated in pregnancy and breastfeeding in some Member States, while in others it is contraindicated only in the third trimester of pregnancy and breastfeeding; furthermore, in some Member States it is contraindicated in the first and third trimester of pregnancy and breastfeeding.

In view of the known risks associated with the use of metamizole, the differences between the product information of metamizole-containing medicines across the EU Member States raise concern. Poland considered that it is in the interests of the Union to harmonise the information regarding maximum daily dose and contraindications in pregnancy and breastfeeding in the product information of all metamizole-containing medicinal products in the EU.

On 26 April 2018, Poland therefore triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess all data available concerning the maximum daily dose and its contraindications on pregnancy and breastfeeding, and issue an opinion as to whether the relevant marketing authorisations should be varied.

## 2. Scientific discussion

### 2.1. Introduction

The active substance metamizole (also referred to as dipyrone) is a non-addictive pyrazole-type analgesic, spasmolytic and antipyretic drug with weak anti-inflammatory effects. Metamizole is available as tablets (film tablet or dispersible), oral drops, solution for injection, and suppositories. It is available as monocomponent but also available in several combination products such as:

- Butylhyoscine/Metamizole;
- Caffeine/Drotaverine/Metamizole Sodium;
- Caffeine/Isometheptene/Metamizole Sodium;
- Caffeine/Metamizole/Orphenadrine Citrate;
- Chlormezanone/Metamizole;
- Diethylpentamid/Metamizole/Propyphenazon;
- Fenpiverinium Bromide/Metamizole Sodium/Pitofenone hydrochloride;
- Hyoscine Butylbromide/Metamizole Sodium;
- Metamizole Sodium/Propyphenazon.

The mechanism of action is not fully understood. Some data suggest that metamizole and its main metabolite 4-methyl-amino-antipyrine (MAA) may have a combined central and peripheral mechanism of action. An inhibition of prostaglandin (PG) synthesis is known, based on interaction with different cyclooxygenases (COX), resulting in changes in the arachidonic acid metabolism. Besides peripheral inhibition of PG synthesis, central activities have been postulated and documented. Nevertheless, the picture of the mode of action remains incomplete until today.

Current indications for metamizole (as single ingredient) include acute severe pain after trauma or surgery, painful colic, tumour pain, other acute or chronic pain, if other therapeutic measures are contraindicated, and high fever, not responding to other measures.

Metamizole has been associated with agranulocytosis (granulocyte counts of less than 500/mm<sup>3</sup>) and anaphylactic shock. Reports on the risk of agranulocytosis associated with the use of metamizol have suggested widely varying estimates. In the 1980s, the International Agranulocytosis and Aplastic Anaemia Study (IAAAS) reported a risk of less than 1.1 per million users within 1 week with a significant regional variability in the rate-ratio estimate (0.8 in Budapest, Hungary and 23.7 in Ulm, West Germany, West Berlin, and Barcelona, Spain) (Kaufmann DW et al. 1986)<sup>1</sup>. In contrast, Hedenmalm and Spigset reported that the risk might be considerably higher (Hedenmalm K and Spiset O 2002)<sup>2</sup>. Based on eight community cases in which the patient was exposed to the drug and 10,892 prescriptions during the period 1995–1999 in Sweden, they estimated an incidence of one case per 1,439 prescriptions. Thus, the potential to induce agranulocytosis may be associated with genetic characteristics of the population studied. The mechanism by which metamizole causes blood disorders has not yet been fully elucidated. Available data suggest an immunological process, as well as direct toxicity towards the progenitor cells in the bone marrow (Tesfa D et al. 2009)<sup>3</sup>.

Whilst metamizole-containing medicinal products were withdrawn in several European countries and also in the USA due to the risk of agranulocytosis, in other countries such as Spain, Poland and Germany, metamizole is frequently used. From the estimates presented by the Sanofi group, well over 8 billion gram metamizole (as single ingredient) have been sold in total in the EU (Austria, Belgium, Croatia, Czech Republic, Germany, Hungary, Italy, Luxembourg, The Netherlands, Norway, Portugal, Romania, Slovakia and Spain) since April 2006, which would correspond to an estimated exposure of over 8 million patient treatment years. The majority of this exposure occurred in Germany (~3.5 million patient treatment years).

## **2.2. Posology and maximum daily dose**

### **2.2.1. Single dose and maximum daily dose – adolescents and adults**

Metamizole has been shown to have a very similar bioavailability after oral or parenteral application with the key pharmacokinetic characteristics being nearly identical. After oral intake, metamizole is rapidly hydrolysed to its main metabolite MAA. The bioavailability of MAA was 85% for tablets, 89% for drops and 87% for the intramuscular injection. In the treatment of elderly patients the AUC is increased 2- to 3-fold. After a single oral administration the half-life of MAA in patients with hepatic cirrhosis increased about 3-fold (Levy M et al. 1995)<sup>4</sup>. The available data for patients with impaired

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1 Kaufman DW, Kelly JP, Levy M, Shapiro S (1986) The drug etiology of agranulocytosis and aplastic anemia. A first report of their relation to drug use with special reference to analgesics. *JAMA* 256:1749–1757.

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

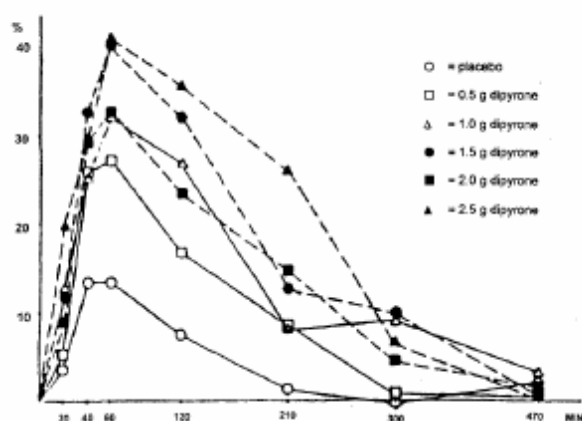
3 Tesfa D, Keisu M, Palmblad J. Idiosyncratic drug-induced agranulocytosis: possible mechanisms and management. *Am J Hematol.* 2009; 84(7): 428–34.

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

renal function show a reduced elimination rate for some other metabolites (AAA and FAA) (German SmPC "Novalgin" Sanofi-Aventis).

Results from one randomized, placebo-controlled, double-blind, PD study, which evaluated doses of 500, 1,000, 1,500, 2,000 and 2,500 mg metamizole administered orally as film-coated tablets to 18 volunteers (Stammberger W 1994)<sup>5</sup> were assessed. Pain attenuation was quantified following constant and painful electrical stimulation of tooth pulp at different time intervals up to 7 hours after drug administration. Tooth pulp stimulation was performed by bipolar stimulation using individually formed impressions of the teeth with controlled current. Verbal pain ratings by the volunteers were used as one of the parameters for the quantification of the analgesic effect, intraindividually comparing the effects of the different doses.

The figure below illustrates the results of the subjective pain ratings. All doses of metamizole had a significantly higher analgesic effect than placebo. Maximal analgesia was observed 1 h after administration of the tablets, independent of the dose. An increase in analgesic effect related to dose was observed at this time, the increase being less pronounced with doses exceeding 1,500 mg. Generally, analgesia persisted longer with increasing dose; however, there was no clear-cut dose response relationship.



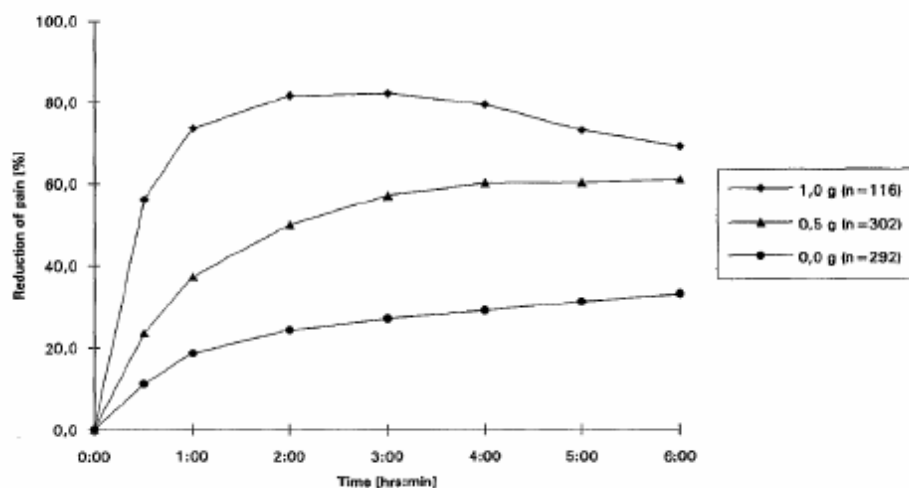
**Figure 1 Dose-response of the analgesic effects of oral metamizole - means of subjective pain ratings (N=18)**

In addition, a meta-analysis on the dose-time-effect relationship of metamizole based on 30 of 33 published studies for post-operative pain and on 12 of 13 published studies for colicky pain (Schinzel S 1994)<sup>6</sup> was assessed. In post-operative pain, two separate analyses were performed, one for the parenteral form (9 out of 22 studies, i.v. and i.m. injections) and one for the tablet formulation (6 out of 8 studies). In colicky pain, all published studies used i.v. administration of metamizole; 6 of the 12 studies were suitable for the meta-analysis. Analyses were based on means of pain level or pain relief recordings since no individual data of patients were available from the publications; in some publications mean values had to be estimated from figure presentations.

The figure below shows the overall means of pain reduction for two different doses of metamizole (500mg and 1000mg) tablets in post-operative pain by time:

5 Stammberger W. Expert report on the pharmacological and toxicological documentation of Novalgin. Sanofi internal document. 1994.

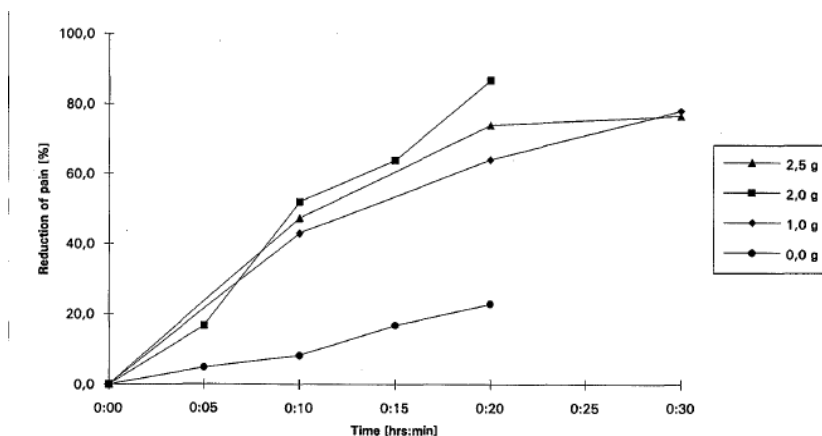
6 Schinzel S. Meta-analysis on the dose-time-effect relationship of Dipyrone (X107). Sanofi internal document. 1994.



**Figure 2 Weighted means of pain reduction in post-operative pain**

It was concluded that 500mg metamizole (one tablet) is an effective oral treatment for moderate to severe post-operative pain. Application of two tablets, i.e. 1,000mg, seems to speed up the onset and to increase the maximum extent of the analgesic effect but does not substantially increase the duration of analgesia.

The figure below shows the overall means of pain reduction in colic pain for three different doses of metamizole (1,000mg, 2,000mg and 2,500mg) given parenterally (i.v.) by time:



**Figure 3 Weighted means of pain reduction in colic pain**

Overall, in colic pain, the analgesic effect of 1,000mg and 2,500mg metamizole 20 minutes after application was similar. However, parenteral application of 2,500mg metamizole (i.v. and i.m.) showed a superior reduction of postoperative pain compared to 1,000mg metamizole during the first 2 hours after application (no figure presented).

Results are in line with a recent Cochrane review (Hearn L et al. 2016)<sup>7</sup>. The authors included eight studies, involving 809 participants, comparing oral metamizole 500 mg (143 participants), oral metamizole 1000 mg (57 participants), and intramuscular metamizole 2000 mg (35 participants) with placebo (236 participants). In addition to placebo, all studies used active controls (ibuprofen, paracetamol, aspirin, flurbiprofen, ketoprofen; 338 participants). Seven studies used the oral route of

7 Hearn L et al. Single dose dipyrone (metamizole) for acute postoperative pain in adults. Cochrane Database of Systematic Reviews. 2016.

administration, and one study used the intramuscular route. The mean age ranged from 23 to 62 years. Six studies included both men and women, and two studies included only women. All the studies were small, but were otherwise considered to be of moderate to good quality. Over 70% of participants experienced the primary outcome of at least 50% pain relief over four to six hours with oral metamizole 500 mg compared to 30% with placebo (five studies, 288 participants; NNT 2.4 [95% CI 1.8 to 3.1]) (moderate quality evidence). There were insufficient data to assess other doses or routes of administration of metamizole. Fewer participants needed rescue medication within four to six hours with metamizole 500 mg than with placebo (7% with metamizole versus 34% with placebo; four studies, 248 participants) (low quality evidence).

From the literature it is emerged that metamizole is mainly used in clinical practice to manage post-operative pain. The prescribed daily dose ranges between 1,500 – 6,000 mg and the average treatment duration is 3-5 days. A study in Germany revealed 33-78% patients after ambulatory surgery, require post-operative analgesia and metamizole was used at the maximal daily dose of 4,000 – 6,000 mg (Engelbrecht JS and Pogatzki-Zahn EM 2010)<sup>8</sup>. Another study of analgesics use in pregnancy, labour and delivery conducted in Germany in 2004 revealed maximum daily dose of metamizole as 500 – 1,000 mg 4 times a day (i.e. 2,000 - 4,000mg). In a retrospective cohort study of outpatients conducted in Sweden in 1999 the maximum prescribed daily dose of metamizole in outpatients was 6,000 mg (Backstrom M et al. 2002)<sup>9</sup>.

There are few reports of metamizole overdosing. One report describes vomiting and red urine after the intake of 49g metamizole. The patient recovered after stomach emptying and forced diuresis without sequelae. Occasionally reversible renal insufficiency has been described (Levy et al. 1995).

A retrospective review of data in a poison centre revealed 243 records of acute metamizole exposure (Bentur Y and Cohen O 2004)<sup>10</sup>. Patients concerned were aged between 4 months and 83 years, with a median age of 17 years. The median amount of metamizole intake was 5g (250mg-45g). In 39 patients a total of 49 toxic events occurred, 57% of them were gastrointestinal (i.e. vomiting, abdominal pain, nausea), all were mild.

Cases in one marketing authorisation holder’s database with daily dose of  $\leq 4,000$  and  $> 4,000$  mg were analysed. The results are presented below:

**Table 1 Overview of cases involving patients aged between 18 and 65 including information on daily dose**

<b>967 cases with dose information and patient’s age between 18-65 years</b>		
	<b>Non-serious cases</b>	<b>Serious cases</b>
<b>830 cases for daily dose: <math>\leq 4</math> g</b>	<b>414 (49.9%)</b>	<b>416 (50.1%)</b>
<b>137 cases for daily dose: <math>&gt; 4</math> g</b>	<b>28 (20.4%)</b>	<b>109 (79.6%)</b>

Out of 967 cases, weight (47- 112kg) was reported in 103 cases. In 86 out of 103 cases patients received dose  $\leq 4$ g (54 non-serious and 32 serious) while and in 17 cases patients received dose  $> 4$ g (2 non-serious, 15 serious).

8 Engelbrecht JS, Pogatzki-Zahn EM. Pain management after ambulatory surgery in Germany. *Anaesthesiol Intensivmed Natfallmed Schmerzther.* 2010, 45 (1), 44-54.

9 Backstrom M et al. Utilization pattern of metamizole in northern Sweden and risk estimates of agranulocytosis. *Pharmacoepidemiology and Drug Safety.* 2002, Vol. 11, 3, pp. 239-245.

10 Bentur Y, Cohen O. Dipyrrone overdose. *J Toxicol* 2004;42(3):261-65.

**Table 2 Overview of cases involving patients aged between 65 and 98 including information on daily dose**

<b>511 cases with dose information and patient's age between 65-98 years</b>		
	<b>Non-serious cases</b>	<b>Serious cases</b>
<b>404 cases for daily dose: ≤ 4 g</b>	<b>156 (38.6%)</b>	<b>248 (61.4%)</b>
<b>107 cases for daily dose: &gt; 4 g</b>	<b>11 (11.3%)</b>	<b>96 (89.7%)</b>

Out of 511 cases, weight was reported in 78 cases, in 58 cases (weight 37-115kg) the patients received dose ≤ 4g (37 non-serious and 21 serious cases), and in 20 cases (range 55-100kg) patients received > 4g (2 non-serious, and 18 serious cases).

The serious cases were not discussed in more detail by the marketing authorisation holder. However, it was concluded that no new safety signal was detected that would justify a change with regard to the maximum daily dose (6,000 mg in Spain) in the current summary of product characteristics and package leaflet.

### **2.2.2. Single dose and maximum daily dose – children**

A randomized comparison of metamizole applied per os or i.m. with oral ibuprofen with regard to antipyretic efficacy was conducted in 75 febrile children (Prado et al. 2006)<sup>11</sup>. The children were randomly assigned to one of 3 treatment groups to receive single doses of 10mg/kg ibuprofen or 15mg/kg metamizole per os or i.m. Fever reduction was recorded 30, 45, 60 and 120 minutes after dosing. After 45 minutes fever had decreased by 0.5°C and by about 1°C after 120 minutes in all 3 groups. Fever-associated symptoms like irritability, crying, anorexia, hyperactivity, chilling and vomiting was improved in all groups. Six patients from the metamizole groups, 4 from the oral and 2 from the i.m. group, and 2 from the ibuprofen group were withdrawn because of vomiting.

For the subpopulation of patients with acute renal colic, a study conducted in 30 patients in Brazil reported that metamizole was administered at a mean dose of 17.9 ± 1.5 mg/kg (Mercado Dublin MF 2011)<sup>12</sup>.

Another study focused on the appropriateness of analgesic doses received by paediatric patients over the period 2004 to 2005. Considering the recommended dosage of metamizole in Brazil of 15 to 20 mg/kg per dose, 89.7% patients treated with metamizole were given an incorrect dose: 15.2% of those were underdosed, and 84.8% were over-dosed (Alves et al. 2007)<sup>13</sup>.

A German study was conducted in six different paediatric centres from September 2013 to September 2014 (Fieler M et al. 2015)<sup>14</sup>. One thousand one hundred and seventy-seven children aged up to six years (mean age 35.8 ± 18.1 months [0.1 to 72 months]) received a single dose of intravenous metamizole for postoperative pain therapy. The studied cohorts included 113 patients (9.9%) younger than 1 year of age and 34 patients (3%) younger than 1 month. Metamizole was administered preoperatively in 28 patients (2.5%), intraoperatively in 1104 patients (96.4%) and postoperatively in

<sup>11</sup> Prado J et al. Antipyretic efficacy and tolerability of oral ibuprofen, oral dipyrrone and intramuscular dipyrrone in children: a randomized controlled trial. Sao Paulo Med J. 2006 May 4;124(3):135-40.

<sup>12</sup> Mercado Dublin MF et al. Acute renal pain treatment in emergency department. European Journal of Pain Supplements. 2011, Vol. 5, 1, p. 144.

<sup>13</sup> Alves JGB et al. Dipyrrone and acetaminophen: Correct dosing by parents? Sao Paulo Medical Journal. 2007, Vol. 125, 1, pp. 57-59.

<sup>14</sup> Fieler M et al. Metamizole for postoperative pain therapy in 1177 children: A prospective, multicentre, observational, postauthorisation safety study. Eur J Anaesthesiol. 2015 Dec;32(12):839-43.



13 patients (1.1%). The mean metamizole dose was  $17.3 \pm 2.9$  mg/kg (8.3 to 29.4 mg/kg). Treatment with single intravenous doses of metamizole was well tolerated.

A recent study investigated the use of intravenous metamizole in 316 infants younger than 1 year undergoing surgery with a particular focus on possible serious ADRs (e.g., hemodynamic, anaphylactic or respiratory reactions, and agranulocytosis). 81 patients were younger than 1 month. In infants treated for postoperative pain, the mean single i.v. dose of metamizole was  $17.8 \pm 3.1$  mg/kg (range: 9.2 to 29.8) (Sümpelmann R et al. 2017)<sup>15</sup>. Treatment with single intravenous doses of metamizole was well tolerated. In particular, no respiratory adverse events directly related to the metamizole administration were reported and hemodynamic parameters remained stable within the physiological range.

### 2.2.3. Conclusion on posology and maximum daily dose

Metamizole is usually applied per os, but parenteral and rectal formulations are available as well. The standard single dose for adults is 500mg. Metamizole has been shown to have a very similar bioavailability after oral or parenteral application with the key pharmacokinetic characteristics being nearly identical. This is reflected in the dosing advice, which does not have significant differences between oral or parenteral (i.v. and i.m.) schedules (Levy M et al. 1995).

Based on the data assessed, the recommended parenteral single dose in adults and adolescents aged 15 years or over is 500 - 1,000 mg. A single dose can be taken up to 4 times daily at intervals of 6–8 hours leading to a maximum daily dose of 4,000 mg. However, based on the dose-time-relationship data discussed above (Schinzel S 1994) it seems appropriate to allow, if necessary, a parenteral single dose of 2500 mg metamizole and a maximum daily dose of 5000 mg metamizole.

The recommended oral single dose in adults and adolescents aged 15 years or over is also 500 to 1,000 mg. A single dose can be taken up to 4 times daily at intervals of 6–8 hours leading to a maximum daily dose of 4,000 mg.

In children and adolescents up to 14 years old, a dose of 8–16 mg metamizole per kg body weight as a single dose is recommended for the originator product. This single dose can be taken up to 4 times daily at intervals of 6–8 hours. Age appropriate formulations (oral drops, solution for injection) are available.

Although it is noted that in some non-EU countries e.g. in Brazil the recommended single dose in paediatric patients is higher than in Europe (15 to 20 mg/kg per dose), the literature data does not justify a change with regard to the single and maximum daily dose in the current product information.

Two recent studies showed that single intravenous doses of metamizole used for prevention or treatment of postoperative pain were safe in more than 400 infants younger than 1 year (Fieler M et al. 2015, Sümpelmann R et al. 2017). Thus, the more intrusive intramuscular injections could be avoided as intravenous administration is seen as a suitable alternative option. In addition, a general rejection of the use of metamizole for administration in infants below the age of 3 months is not considered justified based on the fact that no particular concerns arose from the studies which included patients in this age group.

A literature search performed by the MAHs concerning drug-drug interactions data between the active compounds in the fixed combination medicinal product (Metamizole + Hyoscine buthylbromide; Fenpiverinum + Pitofenone + Metamizole; Caffeine + Drotaverine + Metamizole) did not reveal any significant data. No data was available in relation to fixed combination products and 100 mg and 200

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15 Sumpelmann R et al. Metamizole for Postoperative Pain Therapy in Infants Younger than 1 Year. European Journal of Pediatric Surgery. 2017, Vol. 27, 3, pp. 269-273.

mg suppositories that would support a change in posology/maximum daily dose. These products are not widely authorised in the European Union and availability of data is limited. Therefore no recommendations on posology and maximum daily dose can be issued for these products.

## **2.3. Pregnancy and breastfeeding**

### **2.3.1. Teratogenicity and embryotoxicity**

There are few studies on the outcome of pregnancies exposed to metamizole. The most recent one is that of Dathe based on the German Embryotox pharmacovigilance system (Dathe K et al. 2017)<sup>16</sup>. During the study period 2000 to 2015, the authors prospectively enrolled a cohort of 446 women exposed to metamizole during the 1st trimester. The rate of major birth defects (7/373, 1.9%) was not increased compared to a non-exposed comparison cohort (OR adjusted 1.15, 95% CI 0.4-3.5).

In addition to the prospectively enrolled metamizole cohort, the German Embryotox system received 14 retrospective reports of pregnancies exposed to metamizole during the 1st trimester. Three pregnancies ended as spontaneous abortion, one of these was a twin pregnancy in which one twin aborted, while the other was a healthy female live-born. Of the 12 live-born infants, 10 were affected with heterogeneous birth defects not suggestive for a distinct pattern of anomalies.

The authors concluded "*Metamizole exposure in the 1st trimester does not seem to bear a substantial teratogenic risk. Our study results support reassurance in those instances where metamizole has been used during an unrecognized pregnancy or where its use appears indispensable.*"

Another multi-center cohort study with 108 1st trimester exposed patients also did not observe an increased risk for major birth defects after metamizole use; the 3 reported birth defects included unilateral hydrothorax, atrial septal defect, and micrognathia (Bar-Oz B et al. 2005)<sup>17</sup>.

A population based case-control study of the Hungarian Congenital Abnormality Registry with retrospective maternal self-reported information on drug use found an association between metamizole during the second or third month of pregnancy and congenital diaphragmatic anomalies, cardiovascular malformations, and other heterogeneous isolated abnormalities based on 11, 128 and 38 affected cases, respectively. Such associations could not be confirmed when medical records on metamizole exposure were used instead of maternal self-reports and the authors concluded that the major explanation of their finding may be a "chance effect" (Banhidy F et al. 2007)<sup>18</sup>.

In the Berlin study cohort (Dathe K et al. 2017), only one of the 7 major birth defects affected the heart, and no diaphragmatic anomalies were observed.

A Brazilian study covering 555 pregnant women with metamizole use during pregnancy did not find risk increases for birth defects, intrauterine death, preterm birth and low birth weight in comparison to 4276 women who did not use metamizole. However, the study had several limitations including no differentiation when during pregnancy metamizole was taken, and how long and at which dosage (da Silva Dal Pizzol T et al. 2009)<sup>19</sup>. Furthermore, the authors believed that metamizole use is underreported since it is a widely used over-the-counter medication in Brazil.

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16 Dathe K, Padberg S, Hultsch S, Meixner K, Tissen-Diabaté T, Meister R, Beck E, Schaefer C. Metamizol use during first trimester - A prospective observational cohort study on pregnancy outcome. *Pharmacoepidemiol Drug Saf* 2017; 26: 1197-1204.

17 Bar-Oz, B.; Clementi, M.; Di Gianantonio, E et al: Metamizol (dipyrone, optalgin) in pregnancy, is it safe? A prospective comparative study. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2005; 119: 176-9.

18 Banhidy F, Acs N, Puh E, Czeizel AE: A population-based case-control teratologic study of oral dipyrone treatment during pregnancy. *Drug Saf* 2007; 30:59-70.

19 da Silva Dal Pizzol T; Schler-Faccini L; Mengue SS; Fischer MI: Dipyrone use during pregnancy and adverse perinatal events. *Arch Gynecol Obstet* 2009; 279: 293-7.

With respect to spontaneous pregnancy loss, the Berlin study results on 1st trimester metamizole use do not indicate embryotoxic effects (Dathe K et al. 2017). The cumulative incidence of spontaneous abortions was even lower in the metamizole cohort than in the comparison cohort (12.2% vs 19.4%; HR adjusted 0.72, 95% CI 0.5-1.1). On the other hand, there was an increased rate of elective terminations of pregnancy (ETOP) mostly for “social” reasons (12.5% vs 9.4%; HR adjusted 1.48, 95% CI 0.98-2.2) similar to the findings of Bar-Oz (Bar-Oz B et al. 2005). As with other drugs not recommended for use in pregnancy, fears of metamizole’s risk may play a major role in deciding for ETOP. There was no excess of prenatal diagnoses of malformations explaining the increased ETOP rate in either study cohort.

### **Fetotoxicity**

There are few case reports on metamizole use during the 3<sup>rd</sup> trimester and oligohydramnios (Ortiz Movilla R et al. 2011<sup>20</sup>, Weintraub A et al. 2006<sup>21</sup>, Sanchez de la Nieta MD et al. 2003<sup>22</sup>, Catalan JL et al. 1995<sup>23</sup>) and ductus arteriosus narrowing/constriction (Lopes LM et al. 2016<sup>24</sup>, Ortiz Movilla R et al. 2011<sup>25</sup>, Weintraub A et al. 2006<sup>26</sup>, Marti Sole JJ et al. 1996<sup>27</sup>). In these cases, metamizole exposure occurred during the 3<sup>rd</sup> trimester (the earliest case was week 30; Lopes LM et al. 2016), varied between one single dosage (Schiesl B et al. 2005<sup>28</sup>) and 10 days treatment and daily dosage between 500 and 6,000 mg. In one case, metamizole was given i.v. In some cases, metamizole was combined with scopolamine. Fetal effects were diagnosed within 60 hours after start of exposure. Symptoms improved a few days after cessation of exposure. These fetotoxic effects are similar to those observed in association with 3<sup>rd</sup> trimester use of NSAID such as indomethazine, diclofenac, ibuprofen. On the other hand, it has been shown that metamizole is only weak COX-1 and COX-2 inhibitor without relevant anti-inflammatory properties. Its analgesic action is probably mediated, among others, via central COX-3 inhibition (Jasiecka A et al. 2014)<sup>29</sup>. Interference with ASA induced inhibition of platelet COX-1 indicates that metamizole shares some clinical effects with ibuprofen but with different interactions with the COX system (Hohlfeld T et al. 2013)<sup>30</sup>. However, the exact mode of its complex action is not entirely known to date.

### **Wilms tumor and leukemia**

A case-control study from Brazil is based on 109 children with Wilms tumor and describes a possible correlation with metamizole use during pregnancy (Sharpe CR et al. 1996)<sup>31</sup>. A significant association

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20 Ortiz Movilla R, Álvarez García A, Martínez Bernat L, Alvarez Fernandez B, Toral Vazquez B, Cortes Coto MT.

Administration of metamizol, renal failure and intrauterine ductus arteriosus constriction. An uncommon association. *Acta Pediatr Esp* 2011; 69: 476-8.

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to metamizol was only found after stratification according to the monthly family income in the group of low-income families based on 11 affected children. No details on metamizole exposure such as gestational period, duration, or dosage are provided. Therefore, causality cannot be reasoned from these data. The authors state that other factors as well may have influenced the development of Wilms tumor. There are no other studies or case reports supporting an association between prenatal metamizole and Wilms tumor.

A multi-center study found a significant association between prenatal exposure to several agents, such as herbal medicines, pesticides and also metamizole (based on 12 affected patients), and an increased risk of infant acute leukemia (Alexander FE et al. 2001)<sup>32</sup>.

A study from Brazil covering 202 infants up to 21 months with acute leukemia did not detect an association with metamizole (Pombo-de-Oliveira et al. 2006)<sup>33</sup>.

Polymorphisms of N-acetyltransferase 2 (NAT2) resulting in slow acetylation of metamizole was found associated with increased risk of infant leukemia - however independent of maternal intake of metamizol (Zanrosso CW et al. 2010)<sup>34</sup>.

Another Brazilian multicenter case-control study based on interviews with mothers of 231 leukemic infants aged up to 23 months, 176 with acute lymphocytic leukemia and 55 acute myeloid leukemia, focused on possible effects of analgesic intake during pregnancy and lactation in comparison with 411 children with various nonmalignant diseases. For acute lymphocytic leukemia and based on 56 exposed cases, the exclusive use of metamizole preconception gave an OR of 1.63 (95% CI 1.06-2.53) and during lactation based on 36 exposed cases an OR of 2.00 (95% CI 1.18-3.39). The exclusive use of metamizole during pregnancy did not increase the risk of acute lymphocytic leukemia. Furthermore, there was no association between metamizole and acute myeloid leukemia (Couto AC et al. 2015)<sup>35</sup>.

### 2.3.2. Breastfeeding

One case report describes three cyanotic attacks in an infant of a mother who had taken three doses of 500 mg metamizole 18, 7 and 2 hours, respectively, before the first cyanotic episode. A milk sample and blood samples from both mother and infant were taken 24 hours after the last dose. The concentration of metamizole in milk was 4.3 µg/mL, and the serum concentration was similar in the mother and the infant (3.3 µg/mL and 3.2 µg/mL, respectively) (Rizzoni G and Furlanut M 1984)<sup>36</sup>. Except for a short period of apnea during the 3<sup>rd</sup> episode without alteration in consciousness, clinical appearance and diagnostics were normal including infant follow-up up to 3 years.

Excretion of metamizole in breastmilk including the four main metabolites has also been studied by Zylber-Katz (Zylber-Katz E et al. 1986)<sup>37</sup> in ten lactating women after a single oral dose of 1,000 mg. All 4 metabolites were detected in the breastmilk of all mothers, although only 2 of them show pharmacological activity (MAA and AA; see Jasiocka A et al. 2014)<sup>38</sup>. The total concentration of all 4 metabolites (including the inactive AAA and FAA) averaged 20.5 mg/L at the times sampled.

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32 Alexander FE, Patheal SL, Biondi A et al: Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. *Cancer Res* 2001; 61: 2542-6.

33 Pombo-de-Oliveira MS, Koifman S, Brazilian Collaborative Study Group of Infant Acute Leukemia: Infant acute leukemia and maternal exposures during pregnancy. *Cancer Epidemiol Biomarkers Prev.* 2006; 15: 2336-41.

34 Zanrosso CW, Emerenciano M, Goncalves BA, Faro A, Koifman S, Pombo-de-Oliveira MS. N-acetyltransferase 2 polymorphisms and susceptibility to infant leukemia with maternal exposure to dipyrone during pregnancy. *Cancer Epidemiol Biomarkers Prev* 2010; 19: 3037-43.

35 Couto AC, Ferreira JD, Pombo-de-Oliveira MS, Koifman S; Brazilian Collaborative Study Group of Infant Acute Leukemia. Pregnancy, maternal exposure to analgesic medicines, and leukemia in Brazilian children below 2 years of age. *Eur J Cancer Prev* 2015; 24: 245-52.

36 Rizzoni G, Furlanut M. Cyanotic crises in a breast-fed infant from mother taking dipyrone. *Hum Toxicol* 1984; 3: 505-7.

37 Zylber-Katz E, Linder N, Levy M. Excretion of dipyrone metabolites in human breast milk. *Eur J Clin Pharmacol* 1986; 30: 359-61

38 Jasiocka A, Maślanka T, Jaroszewski JJ. Pharmacological characteristics of metamizole. *Pol J Vet Sci* 2014; 17: 207-14.

Concentration-time curves were presented for two of these mothers, indicating that the peak levels for the different metabolites occurred at 2 to 18 hours post-dose, and none of the metabolites were detected in breastmilk samples after 48 hours (Zylber-Katz E et al. 1986). Using the peak breastmilk concentrations of the active metabolites in these mothers, an exclusively breastfed infant would receive between 6 and 30% of the maternal weight-adjusted metamizole dosage.

A Brazilian multicenter case-control study (see also above) based on interviews with mothers of 231 leukemic infants aged up to 23 months, 176 with acute lymphocytic leukemia and 55 acute myeloid leukemia, focused on possible effects of analgesic intake during pregnancy and lactation in comparison with 411 children with various nonmalignant diseases. For acute lymphocytic leukemia and the exclusive use of metamizole during lactation based on 36 exposed cases an OR of 2.00 (95% CI 1.18-3.39) was calculated. There was no association between metamizole and acute myeloid leukemia (Couto AC et al. 2015).

### **2.3.3. Conclusion on pregnancy and breastfeeding**

Despite being on the market for almost 100 years, data on metamizole during pregnancy and breastfeeding are scarce. This may be due to the fact that in many countries, metamizole is not available. In contrast to common NSAIDs, metamizole is generally not recommended throughout pregnancy. Therefore, exposure rates during pregnancy are probably much lower than of the recommended NSAID ibuprofen which is contraindicated only during the 3<sup>rd</sup> trimester. However, particularly the NSAID indomethacin has been used as tocolytic and by this plenty of observations of fetotoxic effects during the 3<sup>rd</sup> trimester were documented.

Currently there is no evidence of teratogenic or embryotoxic effects of metamizole when used during the 1<sup>st</sup> trimester. However, there is evidence of fetotoxicity in terms of fetal renal impairment and ductus arteriosus constriction when used in the 3<sup>rd</sup> trimester. An association with acute lymphocytic leukemia in infants up to 2 years of age and with Wilms tumor is unlikely but data are insufficient to completely rule out such a risk.

Single doses of metamizole during the 1<sup>st</sup> and 2<sup>nd</sup> trimester are acceptable in selected cases where paracetamol, ibuprofen or diclofenac are not an option. Similar to NSAIDs, metamizole should not be used during the 3<sup>rd</sup> trimester. At least in cases of repeated use during the 3<sup>rd</sup> trimester amniotic fluid and the ductus arteriosus should be controlled by ultrasound and echocardiography. Metamizole should not be used during breastfeeding because the relative infant dose may be high and the overall evidence is scarce. Better-investigated and characterised analgesics should be preferred.

Nevertheless, the very low number of reported serious adverse drug events in pregnancy and lactation over several decades suggest a low overall risk in case of inadvertent or indispensable short term use of metamizole during pregnancy and lactation. Therefore, women should be reassured in such cases along with additional diagnostics if indicated. An overly conservative risk classification could lead to overestimation of risk, unnecessary fears and unjustified clinical decisions which may result in adverse effects in mother and child worse than those observed with metamizole.

## **3. Benefit-risk balance**

Based on the data assessed, the Committee recommended a parenteral single dose in adults and adolescents aged 15 years or over of 500 - 1,000 mg. A single dose can be taken up to 4 times daily at intervals of 6–8 hours leading to a maximum daily dose of 4,000 mg. However, it is appropriate to

allow, if necessary, a parenteral single dose of 2500 mg metamizole and a maximum daily dose of 5000 mg metamizole.

The recommended oral single dose in adults and adolescents aged 15 years or over is also 500 to 1,000 mg. A single dose can be taken up to 4 times daily at intervals of 6–8 hours leading to a maximum daily dose of 4,000 mg.

In children and adolescents up to 14 years old, a dose of 8–16 mg metamizole per kg body weight as a single dose is recommended. This single dose can be taken up to 4 times daily at intervals of 6–8 hours. Age appropriate formulations (oral drops, solution for injection) are available.

The CHMP further noted that two recent studies showed that single intravenous doses of metamizole used for prevention or treatment of postoperative pain were safe in more than 400 infants younger than 1 year (Fieler M et al. 2015, Sumpelmann R et al. 2017). Thus, the more intrusive intramuscular injections could be avoided as intravenous administration is seen as a suitable alternative option. In addition, a general rejection of the use of metamizole for administration in infants below the age of 3 months is not considered to be justified based on the fact that no particular concerns arose from the studies which included patients in this age group.

No data was available to support a change in posology recommendations for the suppository formulations dosed at 100 mg and 200 mg, as well as for the combination products. These products are not widely authorised in the European Union and therefore availability of data is limited.

With regards to pregnancy and lactation, although data is limited there is no evidence of teratogenic or embryotoxic effects of metamizole when used during the 1<sup>st</sup> trimester. However, there is evidence of fetotoxicity in terms of fetal renal impairment and ductus arteriosus constriction when used in the third trimester and so the Committee considered metamizole should be contraindicated during the third trimester.

The Committee also noted that the metabolites of metamizole pass into breastmilk in considerable amounts, and therefore recommended that repeated use of metamizole during breastfeeding should be avoided. In case of a single administration of metamizole, breastmilk should be discarded for a 48-hour period before breastfeeding can be resumed.

## 4. Product Information

The CHMP considered that amendments to sections 4.2, 4.3, and 4.6 of the SmPC were necessary to include the information of this review.

Both the posology and the information regarding use in pregnancy and breastfeeding were harmonised between products.

The Package Leaflet was amended accordingly.

## 5. Grounds for Opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for metamizole-containing medicinal products

- The Committee considered the identified divergences in the product information of metamizole-containing medicinal products, relating to the maximum daily dose and the use of metamizole in pregnancy and breastfeeding.
- The Committee reviewed the totality of the data submitted in relation to the maximum daily dose and the use of metamizole in pregnancy and breastfeeding.
- The Committee that the posology recommendations for metamizole-containing medicinal products should be harmonised. The Committee also considered that metamizole-containing medicinal products should be contraindicated in the third trimester of pregnancy due to the risks of fetal renal impairment and ductus arteriosus constriction.

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

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