

## **Annex II**

### **Scientific conclusions**

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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.

### Overall summary of the scientific evaluation

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.

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 supposed 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 and anaphylactic shock. 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.

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<sup>1</sup>, Sumpelmann R et al. 2017<sup>2</sup>). 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.

### **Grounds for CHMP opinion**

- 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 concluded 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.

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<sup>1</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.

<sup>2</sup> 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.