Office for Registration
of Medicinal Products, Medical Devices and Biocidal Products

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NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

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This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Poland:

INN containing medicinal products	Metamizole containing medicinal products (and related substances)
Active substance(s)	Metamizole sodium
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s) in the referring Member State	1. Zakłady Farmaceutyczne POLPHARMA S.A. 2. Fresenius Kabi Polska Sp. z o.o. 3. AS Kalceks 4. CHEMAX PHARMA Ltd. 5. ADAMED Consumer Healthcare S.A. 6. Wrocławskie Zakłady Zielarskie "Herbapol" S.A. 7. Sopharma Warszawa Sp. z o.o.

Background

Metamizole is a non-addictive pyrazole-type analgesic with analgesic, antipyretic and spasmolytic effects. The mechanism of action is not fully understood. Some data suggest that metamizole and its main metabolite 4-N-methylaminoantipyrine may have a combined central and peripheral mechanism of action.

Metamizole is indicated for severe acute or chronic pain and also for fever which is not responding to other treatment.

During assessment of the new application of the medicinal product containing metamizole, solution for injection, 500 mg/ml, it was found that there was a discrepancy in scope of maximum daily dose of metamizole and contraindications between approved similar products in Poland and across other Member States.

On the 27 of September Poland sent a Non Urgent Information (NUI 19095) "Metamizole sodium (eg. Novalgin) - Discrepancy in scope of maximum daily dose and contraindications".
Above mentioned NUI contained two questions to Member States:
1. What is the maximum daily dose for metamizole containing medicinal products in your country?
2. What are the contraindication concerning pregnancy and breast-feeding for the metamizole containing medicinal products in your country?

According to the information provided by the 25 MS the maximum daily dose in different medicinal products across Member States may differ from 1,5 g to 6 g according to approved Summaries of Product Characteristic.

Contraindications differ considerably too. According to the information provided approved contraindications in medicinal products containing metamizole are:
- third trimester of pregnancy and breastfeeding,
- first and third trimester of pregnancy and breast-feeding,
- pregnancy and breast-feeding.

Issues to be consider

Taking into consideration information mentioned above the maximum daily dose and contraindications concerning pregnancy and breast-feeding are disharmonized among Member States. In Poland's opinion it is in the interests of the Union to harmonize the maximum daily dose and contraindications concerning pregnancy and breast-feeding for the metamizole containing medicinal products in the EU taking into consideration all pharmaceutical forms and whole posology.

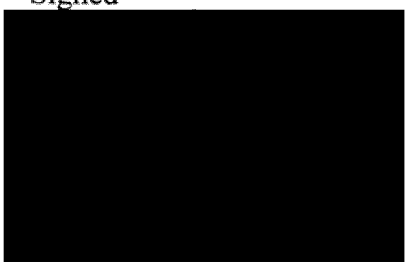
Metamizole was first introduced into clinical use in Germany in 1922 under the brandname "Novalgin" and for many years it was available over-the-counter in most countries, until its toxicities became apparent. Although it is still available over-the-counter in some countries, it is now either a prescription drug or banned in some Member States, due to its potential for adverse events, including agranulocytosis. Serious side effects include agranulocytosis, aplastic anaemia, hypersensitivity reactions (like anaphylaxis and bronchospasm), toxic epidermal necrolysis and it may provoke acute attacks of porphyria, as it is chemically related to the sulfonamides. The relative risk for agranulocytosis appears to greatly vary according to the country of estimates on said rate and opinion on the risk is strongly divided. One meta-analysis that included thousands of patients who were taking this drug, compared the incidence of side effects in patients taking metamizole with an incidence of side effects in patients taking paracetamol and NSAID (1). This meta-analysis showed that patients taking metamizole had no increased risk of serious side effects.

Another study conducted in Poland showed that this drug is completely safe if used for short period of time and in a hospital setting (2,3). In Bulgarian review there is a conclusion that there is sufficient evidence that there is no concern about any currently unknown hazardous potentials of the substance. However, due to risk of agranulocytosis, the duration of therapy should be kept as short as possible (4).

Therefore Polish Competent Authority is of the opinion that there is a need for harmonization in regard to maximum daily dose and contraindications concerning pregnancy and breast-feeding of all medicinal products containing metamizole.

In view of the above and the necessity to take an action at EU level, Poland considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it gives its opinion under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of the medicinal products containing metamizole should be varied.

Signed



Date

2018 -04- 26

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