Divergent positions to CMDh position

Article 107i of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-107i/1537

Metamizole-containing medicinal products

Divergent statement:

The following CMDh Members consider that the benefit-risk balance of metamizole-containing products is negative, based on the following grounds:

- It is well-established that metamizole causes agranulocytosis, an idiosyncratic and unpredictable adverse reaction that can be fatal due to increased susceptibility to infection and sepsis. Clinical management requires a multidisciplinary approach to optimize patient outcomes.
- Due to this risk, metamizole-containing products have had their marketing authorisations withdrawn or were never authorised in several countries such as France, Norway, Denmark, Sweden, UK, US, Canada, and Australia. In countries where metamizole has remained available, cases of metamizole-induced agranulocytosis with fatal outcomes continue to be reported over time, despite implementation of risk minimization measures. Indications for metamizole-containing products include symptomatic treatment of acute pain and/or fever, however there are other treatment options available for pain and fever.
- The conclusion of a positive benefit-risk mainly rests on assuming that the occurrence of metamizole-induced agranulocytosis is extremely rare. However, uncertainty remains regarding the magnitude of the risk with the estimated incidence varying substantially between regions and studies which may reflect methodological limitations or unidentified genetic susceptibility.
- As no clear risk factors for the reaction have been identified, it is not possible to identify measures that can prevent metamizole-induced agranulocytosis. While 30-50% of cases are reported to occur in the first week, time to onset is widely variable, with cases also reported within a day of starting treatment as well as after treatment discontinuation.
- The PRAC recommendations emphasize the importance of awareness of symptoms to facilitate early detection of metamizole-induced agranulocytosis. However, the symptoms may not appear until the onset of infection, are non-specific, overlap with the indications of metamizole such as fever, and furthermore, may be masked by metamizole. In addition to patient cards, blood count monitoring for treatment beyond one week and reduction of pack size, the risk minimisation measures recommended by the PRAC have already been implemented in Finland but have failed to prevent irreversible complications of metamizole-induced agranulocytosis.

In conclusion, the recommended changes to the product information and the DHPC are not considered sufficient to mitigate the risk of metamizole-induced agranulocytosis or the development of related serious complications across the range of indications for which metamizole is currently authorized.

The benefit risk balance of metamizole is therefore considered negative.

CMDh Members expressing a divergent opinion:

Katrine Damkjær Madsen (DK)

Kirsi Haaksiluoto (FI)

Mathilde Geynet-Kovacs (FR)

Nicole Kavanagh (IE)

Christin Olofsson (SE)

Article 107i of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-107i/1537

Metamizole-containing medicinal products

Divergent statement:

The following CMDh Member consider that the benefit-risk balance of metamizole-containing products is negative, based on the following grounds:

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- • The conclusion of a positive benefit-risk mainly rests on assuming that the occurrence of metamizole-induced agranulocytosis is extremely rare. However, uncertainty remains regarding the magnitude of the risk with the estimated incidence varying substantially between regions and studies which may reflect methodological limitations or unidentified genetic susceptibility.
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In conclusion, the recommended changes to the product information and the DHPC are not considered sufficient to mitigate the risk of metamizole-induced agranulocytosis or the development of related serious complications across the range of indications for which metamizole is currently authorized.

The benefit risk balance of metamizole is therefore considered negative.

CMDh Members expressing a divergent opinion:

Suzanne Collett Gordon (NO)

Article 107i of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure No: EMEA/H/A-107i/1537

Metamizole-containing medicinal products

Divergent statement:

The below named CMDh Member considers that next to the measures recommended by PRAC, additional risk minimisation measures are required to ensure a positive benefit-risk balance of oral formulations of metamizole, based on the following grounds:

- • Agranulocytosis is a well-established serious risk of metamizole, which can be fatal. It has an idiosyncratic character, is not dose-dependent, and no risk factors to identify patients at higher risk for developing metamizole-induced agranulocytosis could be identified.
- • Symptoms of agranulocytosis are not specific and may be difficult to recognize by patients, as they can be interpreted as general flu-like symptoms.
- • Considering the above, in order to ensure a positive benefit-risk balance for the concerned products, oral formulations of metamizole-containing products should be subject to a restricted medical prescription by pain specialist in a hospital setting. In addition, additional risk minimisation measures in the form of educational materials for health care providers and patients are needed to aid early recognition and treatment of the serious risk of agranulocytosis. In order to ensure such restricted use of metamizole, a controlled access program is required.

CMDh Members expressing a divergent opinion:

- Priscilla Schoondermark (NL)