13 June 2024
EMA/PRAC/264726/2024

PRAC List of questions

To be addressed by the marketing authorisation holders for metamizole-containing medicinal products

Procedure under Article 107i of Directive 2001/83/EC

Procedure number: EMEA/H/A-107i/1537

INN/active substance: metamizole

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1. Questions

Question 1

Concerning your metamizole-containing medicinal product(s), please provide:

a) information on the type of marketing authorisation(s), marketing status, legal status and approved indication(s), by EEA member state (as per the annexed table),

b) yearly figures on sales and patient exposure from 01 January 2014 until 31 December 2023 (in patient-years based on the WHO defined daily doses (3,000mg)) by product and indication, split by community pharmacy vs. hospital setting if possible, in each EEA member state (as per the annexed table),

c) information included in the summary of product characteristics (SmPC) and package leaflet (PL) regarding the risk of neutropenia/agranulocytosis. Main differences in relation to this risk between the product information (PI) of your medicinal products in the different EU member states should be tabulated (as per the annexed table),

d) a description of any additional risk minimisation measures related to the risk of agranulocytosis/neutropenia in place in each EU member state, as well as the timing of their implementation.

Question 2

Please discuss the effectiveness of the risk minimisation measures in place regarding the risks of agranulocytosis/serious neutropenia and describe the methods that have been used for such evaluation.

Question 3

Please provide an analysis of the available safety data from clinical trials and pharmaco-epidemiological studies (including from published literature) relevant to evaluate the risk of agranulocytosis/serious neutropenia with metamizole-containing medicinal product(s) focusing on:

a) the magnitude of the risk,

b) the time to onset of agranulocytosis/serious neutropenia,

c) the role of underlying infections on the severity and seriousness of agranulocytosis-related complications,

d) the characterisation of possible risk factors (including genetic or other possible predispositions) for serious complications.

Question 4

Based on the above, and taking into account the effectiveness of the current risk minimisation measures, discuss the impact of the risk of agranulocytosis and subsequent infections on the benefit-risk balance of metamizole-containing medicinal product(s) separately in each of the authorised indication(s).

Question 5

Please provide proposals and justifications for further measures to minimise the risk of agranulocytosis/serious neutropenia (including but not limited to changes to the SmPC/PL) that may improve the benefit-risk balance of your metamizole–containing medicinal product(s).

The feasibility of these measures should be discussed, considering the therapeutic indication(s) for which your metamizole-containing medicinal product(s) are used.

Include proposals to monitor the effectiveness of these risk minimisation measures.

2. Additional Data Review

As part of this review, the PRAC considers it necessary to perform an EudraVigilance analysis of all cases of agranulocytosis and serious neutropenia reported between 01 January 2014 and 31 May 2024 for metamizole-containing medicinal products. Cases will be retrieved with the narrow scope of the Standardised MedDRA Query agranulocytosis plus the MedDRA Preferred Term neutropenia. The data to perform this analysis will be provided by EMA and will be evaluated by PRAC together with the responses to the list of questions provided by the MAHs.

Annex

Question 1

a)

Member state	INN	Product name	Type of marketing authorisation	Marketing status	Legal status	Indications

b)

Member state	INN	Product name	Indications	Year	Estimated patient exposure[1]	Sales figures (community pharmacy)	Sales figures (hospital)

[1] Expressed in patient years based on the WHO defined daily doses (3,000mg) and stratified by member state, medicinal product, and split by community pharmacy vs. hospital setting if possible. Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

c)

PI[1]	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Posology (including max daily dose)			
Contraindications			
Warnings and precautions regarding the risks of neutropenia/agranulocytosis			
Interaction with other medicinal products regarding the risks of neutropenia/agranulocytosis			
Undesirable effects regarding the risks of neutropenia/agranulocytosis			

[1] Additional rows should be added as needed to reflect information on the risks of neutropenia/agranulocytosis that may be included in other PI sections.