

**Annex I**

**Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)**

### **Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for metamizole, the scientific conclusions are as follows:

Drug reaction with eosinophilia and systemic symptoms (DRESS)

In view of available data on drug reaction with eosinophilia and systemic symptoms (DRESS) from spontaneous reports and the literature including cases with compatible temporal relationship, a positive de-challenge and/or re-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between metamizole and DRESS is at least a reasonable possibility. The PRAC concluded that the product information of products containing metamizole should be amended accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

### **Grounds for the variation to the terms of the Marketing Authorisation(s)**

On the basis of the scientific conclusions for metamizole the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing metamizole is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing metamizole are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

## **Annex II**

**Amendments to the product information of the nationally authorised medicinal product(s)**

**Amendments to be included in the relevant sections of the Product Information** (new text underlined and in bold, deleted text ~~strike through~~)>

## Summary of Product Characteristics

- Section 4.4

A warning should be amended as follows:

### Severe cutaneous reactions

**Severe** ~~Life-threatening~~ cutaneous adverse reactions (**SCARs**) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and **drug reaction with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal**, have been reported with the use of metamizole **treatment**.

**Patients should be advised of the signs and symptoms and monitored closely for skin reactions.**

If **signs and** symptoms **suggestive of these reactions appear** ~~or signs of SJS, TEN (such as progressive skin rash often with blisters or mucosal lesions), develop~~, metamizole **should be withdrawn** ~~treatment must be discontinued immediately,~~ and must not be re-initiated at any time (**see section 4.3**).

- Section 4.8

Severe cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) **and drug reaction with eosinophilia and systemic symptoms (DRESS)** have been reported in association with metamizole treatment (see section 4.4).

The following adverse reaction(s) should be added under the SOC *Skin and subcutaneous tissue disorders* with a frequency *unknown*:

### **Drug reaction with eosinophilia and systemic symptoms (DRESS)**

## Package Leaflet

2. *What you need to know before you take <Invented name>*:

### *Warnings and precautions*

#### Serious skin reactions

**Serious** ~~Life-threatening~~ skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, **drug reaction with eosinophilia and systemic symptoms (DRESS), have been** ~~are~~ reported **in association** with the use of metamizole treatment. **Stop using metamizole and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.**

**If you have ever developed any severe skin reactions, you must not resume treatment with [Invented name] at any time (see section 4).**

4. *Possible side effects*

Not known

### **Serious skin reactions**

**Stop using metamizole and seek medical attention immediately if you notice any of the following serious side effects:**

- **Reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome, toxic epidermal necrolysis).**
- **Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).**

**Annex III**

**Timetable for the implementation of this position**

### **Timetable for the implementation of this position**

Adoption of CMDh position:	November 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	26 December 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	24 February 2022