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 trimetazidine, the scientific conclusions are as follows:

In view of available data on Drug reaction with eosinophilia and systemic symptoms (DRESS) from spontaneous reports including a close temporal relationship and a positive de-challenge, the Lead Member State considers a causal relationship between trimetazidine and Drug reaction with eosinophilia and systemic symptoms (DRESS) is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing trimetazidine should be amended accordingly.

Moreover, in view of available data from spontaneous reports, including cases with a close temporal relationship and a positive de-challenge, the Lead Member State considers a causal relationship between trimetazidine and paraesthesia is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing trimetazidine should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

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

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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~~)

1. Recommendation on drug reaction with eosinophilia and systemic symptoms (DRESS)

Summary of Product Characteristics

- **Section 4.4 Special warnings and precautions for use**

The following text should be added to the existing place(s) where severe skin reactions (e.g. AGEP) are listed in the existing paragraph regarding severe skin reactions in section 4.4 of the SmPC. If a similar wording is not already in place, it should be entirely implemented. In case the product information already includes a similar or stricter advice on SCARs, the similar or stricter advice remains valid and should remain.

Severe cutaneous adverse reactions (SCARs)

Severe cutaneous adverse reactions (SCARs) including drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with trimetazidine treatment. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, trimetazidine should be withdrawn immediately and an alternative treatment considered (as appropriate).

- **Section 4.8 Undesirable effects**

Skin and subcutaneous tissue disorders SOC

Frequency: Not known - **Drug reaction with eosinophilia and systemic symptoms (DRESS),** acute generalised exanthematous pustulosis (AGEP) **(see section 4.4)**

Package leaflet

- **Section 2 What you need to know before you take <product name>**

Serious skin reactions including drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with <*product name*>. Stop using <*product name*> and seek medical attention immediately if you notice any of the symptoms related to this serious skin reaction described in section 4.

- **Section 4 – Possible side effects**

Stop using <*product name*> and ~~seek medical attention immediately if you notice any of the following symptoms:~~ immediately contact a doctor if you notice any of the following side effects:

Not known: frequency cannot be estimated from the available data

- **Widespread rash, high body temperature, liver enzyme elevations, blood abnormalities (eosinophilia), enlarged lymph nodes and other body organs involvement (Drug Reaction with Eosinophilia and Systemic Symptoms which is also known as DRESS). See also section 2. ~~(DRESS syndrome or drug hypersensitivity syndrome).~~**

- **Serious generalized red skin rash with blistering**

~~(...)~~

~~Frequency unknown:~~

~~- Serious generalized red skin rash with blistering~~

2. Recommendation on paraesthesia

Summary of Product Characteristics

- **Section 4.8 Undesirable effects**

SOC Nervous system disorders

Frequency: Uncommon

Paraesthesia

Package leaflet

Section 4 – Possible side effects

Uncommon side effects: may affect up to 1 in 100 people

● unusual feeling in the skin, such as tingling or a crawling feeling (paraesthesia)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	April 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 June 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	8 August 2024