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 diltiazem, the scientific conclusions are as follows:

a) In view of available data on **lupus-like syndrome** from the literature and spontaneous reports including in some cases a close temporal relationship and a positive de-challenge, the PRAC considers a causal relationship between diltiazem and lupus-like syndrome is at least a reasonable possibility. The PRAC concluded that the product information of products containing diltiazem should be amended accordingly.

b) In view of available data on the drug-drug interaction from the literature, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diltiazem and the drug-drug interaction **(DDI) with lomitapide** is at least a reasonable possibility. The PRAC concluded that the product information of products containing diltiazem should be amended accordingly.

c) In view of available data on **renal failure** secondary to decreased renal perfusion in patients with reduced left ventricular function, severe bradycardia or severe hypotension from the literature, spontaneous reports and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diltiazem and on renal failure secondary to decreased renal perfusion in patients with reduced left ventricular function, severe bradycardia or severe hypotension is at least a reasonable possibility. The PRAC concluded that the product information of products containing diltiazem should be amended accordingly.

d) In view of available data on the risk of **acute kidney injury** secondary to hypotension with diltiazem **overdose** from the literature, spontaneous reports and in view of a plausible mechanism of action, the PRAC considers a causal relationship between diltiazem overdose and the risk of acute kidney injury secondary to hypotension is at least a reasonable possibility. The PRAC concluded that the product information of products containing diltiazem 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 diltiazem the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing diltiazem 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 diltiazem 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 4.3

A contraindication should be added as follows:

Concurrent use with lomitapide (see section 4.5).

- Section 4.4

Warnings should be added as follows:

Close observation is necessary in patients with reduced left ventricular function, bradycardia (risk of exacerbation) or with a 1st degree AV block or prolonged PR interval detected on the electrocardiogram (risk of exacerbation and rarely, of complete block).

Cases of acute renal failure secondary to decreased renal perfusion have been reported in patients with existing cardiac disease especially reduced left ventricular function, severe bradycardia or severe hypotension. Careful monitoring of renal function is advised.

[…]

- Section 4.5

Interactions should be added as follows:

Combination Contraindicated for Safety Reasons

[…]

Ivabradine

Concomitant use with ivabradine is contraindicated due to the additional heart rate lowering effect of diltiazem to ivabradine (see section 4.3)

Lomitapide

Diltiazem (a moderate CYP3A4 inhibitor) may increase lomitapide plasma concentrations through CYP3A4 inhibition leading to increased risk of elevations in liver enzymes (see section 4.3).

[…]

- Section 4.8

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency 'not known':

Lupus-like syndrome

- Section 4.9

The signs and symptoms of overdose should be amended as follows:

The clinical effects of acute overdose can involve pronounced hypotension leading to collapse **and acute kidney injury**, sinus bradycardia with or without isorhythmic dissociation, sinus arrest, atrioventricular conduction disturbances and cardiac arrest.

Package Leaflet

- Section 2

Do not take this medicine if:

You are already taking a medicine containing lomitapide used for the treatment of high cholesterol levels (see section: 'Other medicines and <product name>).

Other medicines and <product name>

In particular, do not take this medicine and tell your doctor if you are taking:

Medicines containing lomitapide used for the treatment of high cholesterol levels. Diltiazem may increase the concentration of the lomitapide that may lead to an increase in the likelihood and severity of liver related side effects.

Warnings and precautions

Talk to your doctor or pharmacist before taking <product name>

If you have a history of heart failure, new shortness of breath, slow heartbeat or low blood pressure. As cases of kidney injury in patients with such conditions have been reported, your doctor may need to monitor your kidney function.

- Section 3

If you take more <product name> than you should

If you take more tablets than you should, tell a doctor or go to a hospital casualty department straight away. Take the medicine pack with you. This is so the doctor knows what you have taken. The following effects may happen: feeling dizzy or weak, blurred vision, chest pain, shortness of breath, fainting, an unusually fast or slow heartbeat, slurred speech, confusion, **decrease of kidney function**, coma, and sudden death.

- Section 4

Possible side effects

Not known: frequency cannot be estimated from the available data

A condition in which the body's defence system attacks normal tissue causing symptoms such as swollen joints, tiredness and rashes (called 'lupus-like syndrome').

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 March 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 May 2023