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 piretanide / ramipril, piretanide, the scientific conclusions are as follows:

In view of available data on life-threatening angioedema from the literature regarding the need to introduce a specific emergency therapy instead of a therapy for histamine-mediated anaphylaxis treatment such as epinephrine, corticoids, antihistamines or H2-receptor antagonists, and also considering the available data on cases of angioedema having occurred following several months or years of treatment, it is recommended to amend the existing warning for the management of this adverse reaction. The product information of piretanide / ramipril containing products 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 piretanide / ramipril, piretanide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing piretanide / ramipril, piretanide 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)

Summary of Product Characteristics

- Section 4.4

The warning should be amended as follows:

Angioedema - head, neck or extremities

If angioedema occurs during treatment, [Product] must be discontinued immediately. Angioedema of the face, extremities, lips, tongue, glottis or larynx ~~were observed~~ ***<u>may occur at any time</u>*** *during therapy with ACE inhibitors.*

~~Emergency treatment~~ ***<u>In case</u>*** *of* ***<u>ACE inhibitors induced</u>*** *~~life-threatening~~ angioedema****<u>, the use of epinephrine may be ineffective</u>*** *~~involves the immediate administration of epinephrine (injected subcutaneously or slowly intravenously) under ECG control and blood pressure monitoring~~. The patient should be hospitalized, monitored for at least 12 to 24 hours and discharged only after the symptoms have subsided completely.*

- Section 4.9

The recommendations for overdose management should be removed as follows:

~~Emergency treatment of angioedema~~

~~In cases of life-threatening angioneurotic edema involving the tongue, glottis and/or larynx, the following emergency measures are recommended: Immediate subcutaneous administration of 0.3 to 0.5 mg epinephrine or slow intravenous administration of 0.1 mg epinephrine (follow dilution instructions!) under ECG and blood pressure control, followed by systemic glucocorticoid administration. Intravenous administration of antihistamines and H2-receptor antagonists is also recommended. In addition to the use of epinephrine, the administration of C1 inactivator may be considered in cases of known C1 inactivator deficiency. The patient should be admitted to hospital and monitored for at least 12 to 24 hours. He should not be discharged until the symptoms have completely subsided.~~

Package Leaflet

Section 2

A warning should be amended as follows:

Warnings and precautions

[…]

Swelling of the head, neck, or hands and feet (angioedema)

If you experience swelling of the face, hands, feet, lips, tongue or throat (angioedema) during treatment with [Product], stop taking the medicine and contact your doctor or nearest hospital immediately. ***<u>This can occur at any time during treatment.</u>***

[…]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2026 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10 May 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	9 July 2026