

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 captopril, the scientific conclusions are as follows:

In view of available data on **Insulin autoimmune syndrome** from the literature, spontaneous reports including in some cases a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between captopril and Insulin autoimmune syndrome is at least a reasonable possibility. The PRAC concluded that the product information of products containing captopril should be amended accordingly.

In view of available data on delayed onset **angioedema** and bradykinin mediated angioedema from the literature, spontaneous reports including in some cases a positive de-challenge the PRAC considers a delayed onset of angioedema relating to captopril treatment is at least a reasonable possibility. The PRAC concluded that the product information of products containing captopril 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 captopril the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing captopril 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

A warning should be added as follows:

Hypersensitivity/angioedema:

Angioneurotic oedema of the extremities, face, lips, mucous membranes, tongue, glottis and/or larynx may occur in patients treated with ACE inhibitors particularly during the first week of treatment. However, in rare cases, severe angioedema may develop after **months or years of** long-term treatment with an ACE inhibitor. Treatment should be discontinued promptly. Angioedema involving the tongue, glottis or larynx may be fatal. Emergency therapy should be instituted.

A warning should be amended as follows:

Insulin Autoimmune Syndrome (IAS):

Cases of Insulin Autoimmune Syndrome (IAS), including severe hypoglycaemic events have been reported during the treatment with captopril (see section 4.8). If IAS is suspected, captopril should be discontinued, and appropriate treatment should be initiated.

Cough:

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- Section 4.8

The following adverse reaction should be added under the SOC 'Immune System Disorder' (frequency not known):

Insulin autoimmune syndrome

Package Leaflet

Section 2

A warning should be amended as follows:

You must tell your doctor if:

[...]

- if you get swelling in your face, neck or throat. **This can occur at any time during treatment.**

[...]

Section 4

The following side effects should be added under the frequency Not known (frequency cannot be estimated from the available data):

Not known: Frequency cannot be estimated from the available data

'disorder of the blood glucose regulating hormones with pronounced lowering of blood sugar levels (insulin autoimmune syndrome)'.

Annex III

Timetable for the implementation of this position

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Adoption of CMDh position:	December 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	25 January 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 March 2026