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 cilazapril, cilazapril / hydrochlorothiazide, the scientific conclusions are as follows:

Based on evidence available, data from literature and likely mechanism regarding the increased risk of angioedema related to pharmacodynamic interactions between angiotensin converting enzyme (ACE) inhibitors and sacubitril/valsartan, racecadotril, mTOR inhibitors and vildagliptin, the PRAC considered that these pharmacodynamic interactions are class effects of ACE inhibitors. Therefore, the product information of cilazapril and cilazapril/hydrochlorothiazide should be updated to advise prescribers and patients of this issue as it could have implications for prevention and management of angioedema.

Furthermore, data from literature, the available evidence and likely mechanism suggest that the pharmacodynamic interactions between ACE inhibitors and ciclosporin, heparin, trimethoprim and trimethoprim/sulfamethoxazole resulting in an increased risk of hyperkalaemia are a class effect of ACE inhibitors. Therefore the product information of cilazapril and cilazapril/hydrochlorothiazide should be updated to advise prescribers and patients of this issue, as it could have implications for prevention and management of hyperkalaemia.

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 cilazapril, cilazapril / hydrochlorothiazide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing cilazapril, cilazapril / hydrochlorothiazide 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 cilazapril, cilazapril / hydrochlorothiazide 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:

Concomitant use with sacubitril/valsartan therapy. Cilazapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see also sections 4.4 and 4.5).

- Section 4.4

Hypersensitivity/angioedema

[...]

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated due to the increased risk of angioedema. Treatment with sacubitril/valsartan must not be initiated earlier than 36 hours after the last dose of cilazapril. Treatment with cilazapril must not be initiated earlier than 36 hours after the last dose of sacubitril/valsartan (see sections 4.3 and 4.5).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk of angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5). Caution should be used when starting racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin in a patient already taking an ACE inhibitor.

[...]

Serum potassium

ACE inhibitors can cause hyperkalemia because they inhibit the release of aldosterone. The effect is usually not significant in patients with normal renal function. However, in patients with impaired renal function and/or in patients taking potassium supplements (including salt substitutes), potassium-sparing diuretics, trimethoprim or co-trimoxazole also known as trimethoprim/sulfamethoxazole and especially aldosterone antagonists or angiotensin-receptor blockers, hyperkalemia can occur. Potassium-sparing diuretics and angiotensin-receptor blockers should be used with caution in patients receiving ACE inhibitors, and serum potassium and renal function should be monitored (see section 4.5).

- Section 4.5

Information on interaction should be added as follows:

Medicines increasing the risk of angioedema

Concomitant use of ACE inhibitors with sacubitril/valsartan is contraindicated as this increases the risk of angioedema (see section 4.3 and 4.4).

Concomitant use of ACE inhibitors with racecadotril, mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and vildagliptin may lead to an increased risk for angioedema (see section 4.4).

[…]

Potassium sparing diuretics, potassium supplements or potassium-containing salt substitutes

Although serum potassium usually remains within normal limits, hyperkalaemia may occur in some patients treated with cilazapril. Potassium sparing diuretics (e.g. spironolactone, triamterene, or amiloride), potassium supplements, or potassium-containing salt substitutes may lead to significant increases in serum potassium. Care should also be taken when cilazapril is co-administered with other agents that increase serum potassium, such as trimethoprim and cotrimoxazole (trimethoprim/sulfamethoxazole) as trimethoprim is known to act as a potassium-sparing diuretic like amiloride. Therefore, the combination of cilazapril with the above-mentioned drugs is not recommended. If concomitant use is indicated, they should be used with caution and with frequent monitoring of serum potassium.

Ciclosporin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with ciclosporin. Monitoring of serum potassium is recommended.

Heparin

Hyperkalaemia may occur during concomitant use of ACE inhibitors with heparin. Monitoring of serum potassium is recommended.

[…]

Package Leaflet

- Section 2

Do not take Cilazapril

If you have taken or are currently taking sacubitril/valsartan, a medicine used to treat a type of long-term (chronic) heart failure in adults, as the risk of angioedema (rapid swelling under the skin in an area such as the throat) is increased.

If you are taking any of the following medicines, the risk of angioedema may be increased:

• Racecadotril, a medicine used to treat diarrhoea;

• Medicines used to prevent organ transplant rejection and for cancer (e.g., temsirolimus, sirolimus, everolimus).

• Vildagliptin, a medicine used to treat diabetes.

In particular, talk to your doctor or pharmacist if you are taking, have recently taken or might take any of the following medicines:

[...]

• Potassium supplements (including salt substitutes), potassium-sparing diuretics and other medicines that can increase the amount of potassium in your blood (e.g. trimethoprim and co-trimoxazole for infections caused by bacteria; ciclosporin, an immunosuppressant medicine used to prevent organ transplant rejection; and heparin, a medicine used to thin blood to prevent clots)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	October 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	1 December 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	30 January 2019