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 / hydrochlorothiazide, the scientific conclusions are as follows:

A signal of increased risk of angioedema with concomitant use of angiotensin converting enzyme (ACE) inhibitors and mammalian target of rapamycin (mTOR) inhibitors was reviewed during this PSUR. ACE inhibitors as well as mTOR inhibitors are known to cause angioedema. A retrospective single centre study reported a higher incidence of angioedema when both class of medicinal products were used compared to an ACE inhibitor alone or mTOR inhibitor alone in patients undergoing kidney transplantation (Mahe, 2007). In a prospective randomized study in long-term hypertension patients, 13 angioedema episodes occurred, all in the group of patients administered everolimus and treated concomitantly with an ACE inhibitor (Stallone, 2004). The authors suggested a dose-dependent synergistic interaction as angioedema were observed only when full doses of both medications were used, and patients tolerated lower doses of these medications without recurrence of angioedema. Five case reports and two cases series reporting concomitant use of ACE inhibitors and mTOR inhibitors and angioedema were further identified in the literature, all reporting a plausible temporal relationship. In view of the accumulating evidence on the interaction between these two classes of medicines, the PRAC considered that patients taking concomitantly mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) and ACE inhibitors may be at increased risk for angioedema and that this information should be included in the product information (PI) of captopril / hydrochlorothiazide-containing medical products.

The results of a non-interventional, population-based, case-control study conducted to determine whether the prescription of co-trimoxazole (sulfamethoxazole/trimethoprim) with an ACE inhibitor or angiotensin receptor blocker was associated with sudden death were published during the reporting period (Fralick, 2014). The primary analysis examined sudden death within seven days of an outpatient prescription for one of co-trimoxazole, ciprofloxacin, norfloxacin, nitrofurantoin, or amoxicillin due to urinary tract infection. The authors concluded that in older patients receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers, co-trimoxazole was associated with an increased risk of sudden death, and they suggest that this association reflects sudden death from co-trimoxazole induced hyperkalemia in a vulnerable group of patients. No increased risk was observed with the other antibiotics. A number of limitations of this study impact the interpretability of the findings. A search in the safety database of one of the MAH identified three cases for captopril mono-component and one for another ACE inhibitor, in concomitant use with co-trimoxazole, all confounded. Trimethoprim and ACE inhibitors are known to induce hyperkalaemia and an additive effect leading to severe hyperkalaemia cannot be ruled out. The PRAC considered that the evidence available, while limited, supports a causal association for an interaction between trimethoprim or co-trimoxazole (trimethoprim/sulfamethoxazole) and an ACE inhibitor leading to severe hyperkalaemia. The PRAC therefore recommends to add these antibiotics to the examples of risk factors in the existing warning on hyperkalaemia, and to reflect the interaction in section 4.5 of the SmPC.

Therefore, in view of the data presented in the reviewed PSUR(s), the PRAC considered that changes to the product information of medicinal products containing captopril / hydrochlorothiazide, were warranted.

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 captopril / hydrochlorothiazide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing captopril / 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 captopril / hydrochlorothiazide are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

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 4.4

[A warning should be added as follows]

Hypersensitivity/angioedema:

Concomitant use of mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus) therapy may be at increased risk for angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) (see section 4.5).

[A warning should be revised as follows]

Hyperkalaemia:

Hyperkalaemia may occur during treatment with an ACE inhibitor. Patients at risk for the development of hyperkalaemia include those with renal insufficiency, diabetes mellitus, hypoaldosteronism or those using concomitant potassium-sparing diuretics, potassium supplements or potassium-containing salt substitutes; or in patients taking other active substances associated with increases in serum potassium (e.g. heparin**, co-trimoxazole also known as trimethoprim/sulfamethoxazole**). If concomitant use of the above mentioned agents is deemed appropriate, regular monitoring of serum potassium is recommended (see section 4.5).

- Section 4.5

[Warnings should be added as follows]

mTOR inhibitors (e.g. sirolimus, everolimus, temsirolimus)

Patients taking concomitant mTOR inhibitors therapy may be at increased risk for angioedema (see section 4.4).

Co-trimoxazole (trimethoprim/sulfamethoxazole)

Patients taking concomitant co-trimoxazole (trimethoprim/sulfamethoxazole) may be at increased risk for hyperkalaemia (see section 4.4).

Package Leaflet

- Section 2

Warnings and precautions

[A warning should be added as follows]

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

[…]

If you are taking any of the following medicines, the risk of angioedema (rapid swelling under the skin in area such as the throat) is increased:

- sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors (used to avoid rejection of transplanted organs)

[…]

Other medicines and <product name>

[Warnings should be added and/or revised as follows]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

[…]

This applies in particular if you are also taking:

[…]

- Medicines which are most often used to avoid rejection of transplanted organs (sirolimus, everolimus and other medicines belonging to the class of mTOR inhibitors). See section "Warnings and precautions".

- Potassium supplements or salt substitutes containing potassium, diuretics (water tablets, in particular those so called potassium sparing), other drugs which can increase potassium in your body (such as heparin **and co-trimoxazole also known as trimethoprim/sulfamethoxazole**).

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2016 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 January 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	29 March 2017

APPENDIX I

PRAC PSUR Assessment Report