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 indapamide, the scientific conclusions are as follows:

Erectile dysfunction

In view of available data on erectile dysfunction from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and re-challenge, the PRAC considers a causal relationship between indapamide and adverse reaction erectile dysfunction is at least a reasonable possibility.

Hypomagnesaemia

In view of available data on hypomagnesaemia from the literature, spontaneous reports including in some cases a close temporal relationship, positive de-challenge, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between indapamide and adverse reaction hypomagnesaemia is at least a reasonable possibility.

Hypochloraemia

In view of available data on hypochloraemia from the literature, spontaneous reports including in some cases a close temporal relationship, a positive de-challenge, and in view of a plausible mechanism of action, PRAC considers a causal relationship between indapamide and adverse reaction hypochloraemia is at least a reasonable possibility.

Hypokalaemia

In view of available data on hypokalaemia from clinical trials, the literature, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between indapamide and hypokalaemia is established.

Hyponatraemia

In view of available data on hyponatraemia from clinical trials, the literature, and in view of a plausible mechanism of action, the PRAC considers a causal relationship between indapamide and hyponatraemia is established.

The PRAC concluded that the product information of products containing indapamide 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 indapamide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing indapamide 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 indapamide 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 4.4

A warning should be added as follows:

Plasma potassium:

Detection of hypokalaemia requires its correction. **Hypokalaemia found in association with low serum magnesium concentration can be refractory to treatment unless serum magnesium is corrected.**

Plasma magnesium:

Thiazides and related diuretics including indapamide have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesaemia (see section 4.5 and 4.8).

- Section 4.5

The interactions should be amended as follows:

Digitalis preparations:

Hypokalaemia **and/or hypomagnesaemia** ~~predisposing~~ **predispose** to the toxic effects of digitalis. Monitoring of plasma potassium, **magnesium** and ECG is recommended and, if necessary, adjusting the treatment.

- Section 4.8

Summary of safety profile

The most commonly reported adverse reactions are **hypokalaemia**, hypersensitivity reactions, mainly dermatological, in subjects with a predisposition to allergic and asthmatic reactions and maculopapular rashes.

~~For indapamide 1.5mg~~
~~During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/l) was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.~~
~~For indapamide 2.5mg~~
~~During clinical trials, hypokalaemia (plasma potassium <3.4 mmol/l) was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.~~
~~The majority of adverse reactions concerning clinical or laboratory parameters are dose-dependent.~~
SOC Metabolism and nutrition disorders

The frequency of the adverse reaction hypokalaemia should be changed to “common”:~~Potassium depletion with hypokalaemia, particularly serious in certain high risk populations~~ **Hypokalaemia** (see section 4.4), frequency ~~Not known~~ **Common**

The frequency of the adverse reaction hyponatraemia should be changed to “uncommon”:Hyponatraemia (see section 4.4), frequency ~~Not known~~ **Uncommon**

The following adverse reactions should be added under the SOC Metabolism and nutrition disorders with a frequency “rare”:

SOC Metabolism and nutrition disorders

- **Hypochloraemia,** frequency **Rare**
- **Hypomagnesaemia**, frequency **Rare**

The following adverse reactions should be added under the SOC Reproductive system and breast disorders with a frequency “uncommon”:

SOC Reproductive system and breast disorders:

- **Erectile dysfunction**, frequency **Uncommon**

Description of selected adverse reactions
During phase II and III studies comparing indapamide 1.5mg and 2.5mg, plasma potassium analysis showed a dose-dependent effect of indapamide:

- **Indapamide 1.5mg: Plasma potassium <3.4 mmol/l was seen in 10 % of patients and < 3.2 mmol/l in 4 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.23 mmol/l.**
- **Indapamide 2.5 mg: Plasma potassium <3.4 mmol/l was seen in 25 % of patients and < 3.2 mmol/l in 10 % of patients after 4 to 6 weeks treatment. After 12 weeks treatment, the mean fall in plasma potassium was 0.41 mmol/l.**

Package Leaflet

Section 4:

Common (may affect up to 1 in 10 people):

- **Low potassium in the blood**

Uncommon (may affect up to 1 in 100 people):

- **Low sodium in the blood that may lead to dehydration and low blood pressure**
- **Impotence (inability to obtain or maintain an erection).**

Rare (may affect up to 1 in 1000 people):

- **Low chloride in the blood**
- **Low magnesium in the blood**

Not known (frequency cannot be estimated from the available data):

- ~~low potassium in the blood,~~
- ~~low sodium in the blood that may lead to dehydration and low blood pressure,~~

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	July CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	6 September 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 November 2021