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 potassium para aminobenzoate the scientific conclusions are as follows:

DRESS

Two well documented literature reports were reported with the use of Potaba. These two literature reports include a close temporal relationship and a positive de-challenge in both cases.

Potassium-paraaminobenzoic acid (Potaba®)-associated DRESS syndrome

Antje Viehweg, Annette Stein, Andrea Bauer, Petra Spornraft-Ragaller, Dermatitis.Sep-Oct 2013;24(5):257-8. doi: 10.1097/DER.0b013e3182a5d880.

The first case describes a 73-year-old man who developed a generalized rash with eosinophilia and elevated liver transaminases two weeks after initiating oral therapy with Potaba. Viral hepatitides were excluded as well as Epstein-Barr virus and cytomegalovirus. According to the authors, the three main criteria of DRESS according to RegiSCAR were fulfilled. In addition, the result of the skin biopsy showed an image consistent with a drug reaction. After withdrawn of Potaba and initiation of corticosteroids the skin reaction subsided rapidly and the liver enzymes went to normal 10 weeks after onset of exanthema.

Potassium Para-aminobenzoate (Potaba) induced DRESS syndrome. A case report

Georgiadis C. , Gkekas C., Kalyvas V., Symeonidis E.N., Papadopoulos D., Malioris A., Papathanasiou M.; HELLENIC UROLOGY VOLUME 31 | ISSUE 2

The second cases describes a 45 year old male with a unremarkable medical history, who did not take any medication and did not report any allergies. Six weeks after the initiation of Potaba, he developed fever and a generalized, itching, morbilliform rash which gradually went diffuse covering his trunk and upper extremities. He also suffered from cervical lymphadenopathy and symptoms of jaundice and his laboratory tests were significant for peripheral eosinophilia and liver damage. Viral hepatitides were excluded as well as Epstein-Barr virus and cytomegalovirus. According to the authors, based on the RegiSCAR criteria (Table 2) and taking into consideration the patient's medical history the diagnosis of drug induced hypersensitivity reaction with visceral involvement was made and attributed to Potaba.

After withdrawal of POTABA and high dose corticosteroids, he responded promptly to the management and his symptoms started improving within 5 days on corticosteroids. His transaminases returned to normal levels on day 18. Four weeks after discontinuation of POTABA he had fully recovered.

In view of available data on the risk of drug reaction with eosinophilia and systemic symptoms (DRESS) from the two literature reports including both a close temporal relationship and a positive de-challenge, the Lead Member State considers a causal relationship between Potaba and DRESS is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing potassium para aminobenzoate should be amended accordingly.

Hypersensitivity reaction including immunoallergic hepatitis

The MAH presented a short evaluation of 35 hypersensitivity-related cases (34 male; 1 female). All 35 cases were assessed by the MAH as valid, and the causality as possible due to pharmacological and temporal relationship in all cases:

"In terms of plausibility, case DE-CHEPLA-C20131483 (a literature case) seems to be the most compelling. In addition to a positive de-challenge and a positive re-challenge, the authors also reported positive results for allergy testing as well as a skin biopsy histologically compatible with acute exanthema and contact eczema. Symptom onset for the re-challenge (disseminated, erythematous rash) occurred after 3 days compared to 4 weeks for the initial episode (generalized rash), suggesting immunological sensitisation. Furthermore, treatment after the second episode with methylprednisolone, a corticosteroid with potent immunosuppressive and anti-inflammatory properties, seems to have been effective based on the reported course of events. This further supports an immunologically mediated hypersensitivity reaction as cause for the reported reactions. Among the cases assessed as serious, case DE-CHEPLA- C20131519 (reported by a physician) has a similar level of plausibility, with repeated positive de- challenge and positive re-challenge as well as treatment with antihistamines and corticosteroids reported as leading to recovery. In case DE-CHEPLA-C20181765 (reported by a consumer), the same symptom (nettle rash) was reported for 3 separate episodes of taking POTABA-GLENWOOD®. The latter two episodes had a very close temporal connection (2 days) between start of therapy and onset of symptoms compared to the initial episode (6 weeks), suggesting immunological sensitisation similar to case DE- CHEPLA-C20131483.

In summary, this cumulative review indicates that there is a significant number of case reports with a plausible relationship between administration of POTABA-GLENWOOD® and hypersensitivity-related reactions, with 43 % of cases reporting a positive de-challenge, a positive re-challenge and/or a positive allergy test as additional support of causality. "

With regard to hepatobiliary reactions, a total of 16 of those hypersensitivity-related cases also comprised a report of liver involvement, with 10 cases reporting increased liver enzymes of various specifications, 3 cases reporting hepatitis, and 3 cases reporting liver injury, hepatocellular injury or liver disorder. There was an overlap between various forms of rash and liver involvement in 8 cases. Liver-related reactions were also reported in 2 out of 3 cases of urticaria and in 2 out of 3 cases of allergic dermatitis. Overall, 12/24 cases of rash/ urticaria/ allergic dermatitis were accompanied by a report of liver involvement. Based on the reported reactions in the examined cumulative data, rash/ urticaria/ allergic dermatitis with concomitant fever was accompanied by liver involvement in 8 of 9 cases (89 %) while liver reactions were reported in only 4 of 15 cases (27 %) of rash/ urticaria/ allergic dermatitis without concomitant fever. Fever is by far the most frequent externally detectable sign suggestive of immunoallergic hepatitis in cases of rash/ urticaria/ allergic dermatitis, in contrast to nausea, jaundice or fatigue which were reported less often. Furthermore, all but one report of a hypersensitivity reaction accompanied by these symptoms additionally included fever as reaction. Thus, the combined appearance of rash/ urticaria/ allergic dermatitis and fever seems to be highly indicative of drug induced immunoallergic hepatitis, differentiating this condition from hypersensitivity-related skin conditions without liver involvement.

In those 8 cases of rash/ urticaria/ allergic dermatitis accompanied by fever and liver involvement, the time between start of treatment with POTABA-GLENWOOD® and onset of reactions was reported as up to 1 month in 2 cases, up to two months in 4 cases, up to three months in 1 case and not reported in 1

case. A time to onset of less than 8 weeks is given by LiverTox as one criterion for definition of drug induced immunoallergic hepatitis. The fact that 6 of 7 of those cases with reported time to onset fulfil this criterion further supports the assumption that the occurrence of rash/ urticaria/ allergic dermatitis with concomitant fever probably indicates drug induced immunoallergic hepatitis.

In view of available data on the risk of Hypersensitivity reaction including immunoallergic hepatitis from the literature and post-marketing reports with a close temporal relationship and a positive de-challenge/re-challenge, the Lead Member State considers a causal relationship between POTABA-GLENWOOD® and Hypersensitivity reactions including immunoallergic hepatitis is at least a reasonable possibility. The Lead Member State concluded that the product information of products containing potassium para aminobenzoate 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 potassium para aminobenzoate the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing potassium para aminobenzoate 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 potassium para aminobenzoate 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)

The following changes to the product information of medicinal products containing the active substance potassium para aminobenzoate are recommended (new text **underlined and in bold**, deleted text ~~strike-through~~). The changes are based on the German product information. For a better overview of paragraph 4.4, headings should also be added:

Summary of Product Characteristics

Section 4.4

Hypersensitivity reactions

Potassium para aminobenzoate must be discontinued immediately if ~~allergic reactions occur~~ **signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle pain , blisters, oral lesions, oedema and eosinophilia)** and must not be restarted.

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions (SCARs) manifesting as drug reactions with eosinophilia and systemic symptoms (DRESS), which can be life-threatening or fatal, have been reported in association with potassium para aminobenzoate treatment. At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of this reaction appear, potassium para aminobenzoate should be withdrawn immediately.

If the patient has developed DRESS with the use of potassium para aminobenzoate, treatment with potassium para aminobenzoate must not be restarted in this patient at any time.

Food intake

Continued intake despite vomiting or insufficient food intake can lead to hypoglycaemia. This is particularly important in the presence of diabetes mellitus.

Renal disease

Reduced kidney function is associated with the risk of hyperkalemia. **Potassium para aminobenzoate** should therefore be used with caution in cases of impaired kidney function and other conditions that are often associated with hyperkalemia.

Liver function

In all patients taking **potassium para aminobenzoate** frequently (at least 4-weekly) liver function tests (transaminases, gamma-GT, AP, LDH, bilirubin) must be performed. If liver function tests are elevated, **potassium para aminobenzoate** must be discontinued immediately.

Section 4.8

Summary of safety profile:

Drug reaction with eosinophilia and systemic symptoms (DRESS) has been reported in association with potassium para aminobenzoate treatment.

Table of ADRs

Skin and subcutaneous tissue disorders:

Uncommon: skin rash (exanthema, eczema, dermatitis, **urticaria**), pruritis

Not known: Drug reaction with eosinophilia and systemic symptoms (DRESS)

Immune system disorders

Not known:

hypersensitivity reactions, including immunoallergic hepatitis (characterized by fever, rash, oedema, arthralgia/myalgia, elevated liver enzymes) (see section 4.4)

Package Leaflet

Section 2

DO NOT TAKE Potaba POTABA-GLENWOOD®:

- **If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking POTABA-GLENWOOD®.**

Warnings and precautions:

Please talk to your doctor or pharmacist before taking POTABA-GLENWOOD®.

Special caution is required,

...

- **if you notice any of the symptoms related to these serious skin reactions described in section 4, stop using POTABA-GLENWOOD® and seek medical attention immediately.**

Section 4

Stop using POTABA-GLENWOOD® and seek medical attention immediately if you notice any of the following symptoms:

- **Widespread rash, high body temperature and enlarged lymph nodes (drug reaction with eosinophilia and systemic symptoms; DRESS syndrome or drug hypersensitivity syndrome).**
- **Allergic reactions, including severe rash or rash accompanied by raised liver enzymes, fever, general malaise, fatigue, muscle pain, blisters, oral lesions, swelling of the skin.**

Uncommon:

Skin rash (including widespread rash, eczema, skin inflammation, chills), itching

Not known:

DRESS syndrome or drug hypersensitivity syndrome

(Already included in the package leaflet:

Section 2: *In all patients taking POTABA-GLENWOOD® liver function tests must be performed regularly, at least monthly. If elevation of liver function tests occurs POTABA-GLENWOOD® must be stopped immediately.*

Section 4: *Allergic skin rash, joint-/muscle pain, elevation of liver enzymes up to jaundice, probably caused by a hypersensitivity reaction*)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	10/2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29/11/2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	20/01/2021