Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for deoxycholic acid, the scientific conclusions are as follows:

A Clinical Trial Database comprehensive review of scar events was performed based on cumulative data collected from all 16 completed interventional ATX-101 studies. Eleven cases were retrieved from Clinical trials (10 cases in treatment group and 1 case in placebo group). In three of them the subjects experienced Scar, in two cases Injection site scar was reported, five subjects experienced Injection site fibrosis and one subject reported Injection site scab. In the three cases where the Scar and Injection site scar events were considered related to the study drug, the subjects experienced previously Injection site ulcer.

Results from a cumulative search of the Allergan's Global Safety Database yielded 43 cases indicative of scarring events of which the majority reported PTs (top 5) were: Injection site scar (11 cases), Scar (7 cases), Injection site scab (6 cases), Indentation (4 cases) and Injection site atrophy (3 cases). In 11 cases skin scarring developed following either Injection site ulceration, necrosis/Soft tissue necrosis or, in one case, Skin lesion. The association between medication errors and injection site scar was evaluated in 8 cases. Three cases did not report events relevant for the scar signal assessment and were not included in the data analysis.

Two literature articles reporting injection site scarring were found. In one article, (Ramirez et al. 2019) two cases are presented, where permanent AEs occurred after DCA injection including an eschar, hypertrophic scar and permanent depressed scars. One of the patients presented developed a "wound and eschar" days after the injection. In a second patient, one month after the second treatment session, multiple depressed scars on the patient's anterior neck, most noticeable when the patient's neck was hyperextended, corresponding to the injection sites of DCA, were noticed. In a second literature article (Sachdev et al.2018), the authors describe the event of an indurated erythematous linear plaque along the mandible, following DCA injection into the facial artery causing skin necrosis.

Based on cumulative review of available data and biological plausibility, there is sufficient evidence of a causal association between the occurrence of Injection site scarring and the use of deoxycholic acid. Based on this evaluation, it is recommended that the event of Injection site scarring will be added to the Product information. The MAH proposed to list this ADR with frequency uncommon based on clinical trial data.

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 deoxycholic acid the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing deoxycholic acid 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 deoxycholic acid are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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 products

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

- **4.4 Special warnings and precautions for use**

<…>

Injections in or near vulnerable areas

<…>

Care should be taken to avoid inadvertent intradermal or intramuscular injection. Belkyra should be injected mid-way into the preplatysmal subcutaneous fat tissue in the submental area. Inappropriate injection techniques such as superficial injections, injections into blood vessels and injections without the skin marking grid, may result in skin ulceration and necrosis **as well as scarring (see section 4.8)**. During injection the needle should not be withdrawn from the subcutaneous fat, as this could increase the risk of intradermal exposure and potential skin ulceration and necrosis. Belkyra should never be re-administered if injection site ulceration or injection site necrosis occurs.

- **4.8 Undesirable effects**

The following adverse reaction(s) should be added under the SOC General disorder and administration site conditions with a frequency 'uncommon':

General disorder and administration	Uncommon	Injection site: Alopecia, urticaria, ulcer, hypersensitivity, **scar****

<…>

**** Injection site scarring has been reported as a result of skin ulceration or necrosis (see section 4.4) and as post-injection scar tissue.**

Package Leaflet

Package Leaflet

- **2. What you need to know before you use BELKYRA**

<…>

Tissue damage around the treatment area (i.e., skin erosion, ulceration, necrosis) can occur. **This can result in scarring.** If ulceration or necrosis occur, you should never be given treatment with Belkyra again (see section 4 Possible side effects).

~~These side effects have all fully resolved without permanent effects and without treatment.~~

- **4. Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

- Temporary nerve injury in the jaw, leading to an uneven smile or facial muscle weakness, can occur.
- Tissue damage around the treatment area (i.e., skin erosion, ulceration, necrosis) can occur. **This can result in scarring.**

If you experience any of the above side effects, contact your doctor or nurse immediately.

<…>

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

Injection site reactions:

- <…>
- **Scar**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position :	24 January 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 March 2021