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 deoxycholic acid, the scientific conclusions are as follows:

A signal regarding injection site necrosis raised during the interval and a cumulative review (up to 29 April 2018) retrieved 39 cases, of which 19 cases concerned skin necrosis (8 serious) and 23 cases reported skin ulceration (4 serious). Taking into account the localisation of necrosis in or near the submental area, the temporal association and the plausible mechanism, a causal association between deoxycholic acid and both injection site necrosis and injection site artery necrosis is an at least reasonable possibility. Therefore PRAC recommends an update of the product information, an update of the educational material and a Direct Healthcare Professional Communication to inform relevant healthcare professionals on the risk of injection site necrosis.

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 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

The warning should be revised as follows:

Care should be taken to avoid inadvertent intradermal or intramuscular injection. **<product name>**~~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.** ~~Do not withdraw~~ **During injection** the needle **should not be withdrawn** from the subcutaneous fat ~~during injection~~, as this could increase the risk of intradermal exposure and potential skin ulceration **and necrosis. <product name> should never be re-administered if injection site ulceration or injection site necrosis occurs.**

- Section 4.8

The following adverse reactions should be added under the SOC General disorders and administration site conditions with a frequency not known:

Injection site necrosis

Injection site artery necrosis

The following information is proposed to be included as a footnote for the adverse reaction of injection site necrosis:

Adverse reactions related to injection site necrosis were reported as fat necrosis, necrosis, skin necrosis and soft tissue necrosis. These events occurred around the treatment area with affected area ranging between 0.5 cm and 3 cm. In rare cases, the entire submental area was affected.

Package Leaflet

Warnings and precautions should be revised in line with the SmPC proposal:

Section 2. What you need to know before you use <Product name>

Warnings and precautions

[…]

• ~~Temporary~~ Tissue damage **around the treatment area** (i.e., skin erosion**, ulceration, necrosis**) can occur ~~if Belkyra is injected into structures other than subcutaneous fat~~. ~~Therefore Belkyra has to be administered only subcutaneously.~~ **If ulceration or necrosis occur, you should never be given treatment with <product name> again (see section 4 Possible side effects).**

Section 4. Possible side effects

The following side effects should be added in line with the SmPC proposal:

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

[…]

• ~~Temporary~~ Tissue damage **around the treatment area** (i.e., skin erosion, **ulceration, necrosis**) can occur ~~if <Product name> is injected into structures other than subcutaneous fat. Therefore <Product name> has to be administered only subcutaneously.~~

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

[…]

Side effects where the frequency is not known:

• **Injection site reaction: tissue damage and cell-death (necrosis) around the treatment area**

Annex III

Conditions to the Marketing Authorisation(s)

National competent authorities of Member State(s) or reference Member State(s), if applicable, shall ensure that the following conditions are fulfilled by the MAH(s):

Conditions	**Date**
The Marketing Authorisation Holders of deoxycholic acid and related substances shall develop and submit educational materials according to agreed core elements. These materials should ensure that prescriber are informed and the patients understand and acknowledge the risks associated with deoxycholic acid. These should be submitted to the National Competent Authorities:	Within 3 months of finalisation of the current procedure.

Annex IV

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	12 December 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	26 January 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	27 March 2019