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 isotretinoin (oral formulations) the scientific conclusions are as follows:

In view of available data on **sacroiliitis** from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers a causal relationship between isotretinoin and sacroiliitis is at least a reasonable possibility. The PRAC concluded that the product information of products containing isotretinoin should be amended accordingly.

In view of available data on **dry eye** from the spontaneous reports and in view of a plausible mechanism of action, the PRAC considers a causal relationship between isotretinoin and persistent dry eye is at least a reasonable possibility. The PRAC concluded that the product information of products containing isotretinoin should be amended accordingly.

In view of available data on **urethritis** from the literature and spontaneous reports including in some cases a close temporal relationship, a positive de-challenge and rechallenge, in view of a plausible mechanism of action, the PRAC considers a causal relationship between isotretinoin and urethritis is at least a reasonable possibility. The PRAC concluded that the product information of products containing isotretinoin 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 isotretinoin (oral formulations) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing isotretinoin (oral formulations) 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 isotretinoin (oral formulations) 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:

Musculo-skeletal and connective tissue disorders

Sacroiliitis has been reported in patients exposed to isotretinoin. To differentiate sacroiliitis from other causes of back pain, in patients with clinical signs of sacroiliitis, further evaluation may be needed including imaging modalities such as MRI. In cases reported post-marketing, sacroiliitis improved after discontinuation of <product name> and appropriate treatment.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Musculoskeletal and connective tissue disorders with a frequency unknown:

Sacroiliitis

Package Leaflet

- Section 2

Talk to your doctor if you experience persistent pain in your lower back or buttocks during treatment with <product name>. These symptoms may be signs of sacroiliitis, a type of inflammatory back pain. Your doctor may discontinue treatment with <product name> and refer you to a specialist for treatment of inflammatory back pain. Further evaluation may be needed including imaging modalities such as MRI.

- Section 4

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

Sacroiliitis, a type of inflammatory back pain causing pain in your buttocks or lower back

Summary of Product Characteristics

- Section 4.4

The warning should be amended as follows:

Dry eyes, corneal opacities, decreased night vision and keratitis usually resolve after discontinuation of therapy. **Cases of dry eyes not resolving after discontinuation of therapy have been reported.** Dry eyes can be helped by the application of a lubricating eye ointment or by the application of tear replacement therapy. Intolerance to contact lenses may occur which may necessitate the patient to wear glasses during treatment.

Package leaflet

- Section 2

The warning should be amended as follows:

Isotretinoin may cause dry eyes, intolerance to contact lenses and visual difficulties including decreased night vision. **Cases of dry eyes not resolving after discontinuation of therapy have been reported.** Tell your doctor if you have any of these symptoms. Your doctor may ask you to use lubricating eye ointment or tear replacement therapy. If you use contact lenses and you have developed intolerance to contact lenses, you may be advised to wear glasses during the treatment. Your doctor may refer you to a specialist for advice if you develop visual difficulties and you may be asked to stop taking Isotretinoin.

Summary of Product Characteristics

- Section 4.8

The following adverse reaction(s) should be added under the SOC Renal and urinary disorders tissue disorders with a frequency unknown:

Urethritis

PIL

- Section 4

The following adverse reaction(s) should be added under Other side effects with a frequency unknown:

Inflammation of the urethra

Annex III

Timetable for the implementation of this position

Timetable for the implementation of the agreement

Adoption of CMDh position:	December 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	30 January ~~2021~~2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	31 March ~~2021~~2022