

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 anal fissure from the literature, spontaneous reports including in some cases a close temporal relationship, a positive re-challenge and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between isotretinoin and anal fissure 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 acute generalized exanthematous pustulosis (AGEP) from the literature, spontaneous reports including cases a close temporal relationship, a positive de-challenge and in view of a plausible mechanism of action, the PRAC considers that a causal relationship between isotretinoin and AGEP is at least a reasonable possibility. The PRAC concluded that the product information of products containing isotretinoin should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

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 recommends that the terms of the marketing authorisation(s) should be varied.

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 amended as follows:

Erythema multiforme (EM), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), **and acute generalized exanthematous pustulosis (AGEP)**, which can be life-threatening or fatal, have been reported in association with <medicine> treatment (see section 4.8).

Patients should be advised of the signs and symptoms of the severe cutaneous adverse reactions and should seek medical advice from their physician immediately when observing any indicative signs or symptoms.

If signs and symptoms suggestive of these reactions appear, <medicine> should be withdrawn immediately and an alternative treatment considered (as appropriate).

If the patient has developed a severe cutaneous adverse reaction such as SJS, TEN, or AGEP or with the use of <medicine>, treatment with <medicine> must not be restarted in this patient at any time.

Section 4.8

The following adverse reaction should be added under the SOC Skin and subcutaneous tissue disorders with a frequency "not known":

Acute generalized exanthematous pustulosis (AGEP)

The following adverse reaction should be added under the SOC "Gastrointestinal Disorders" with a frequency "not known":

anal fissure

Package Leaflet

Section 2 - What you need to know before you use <medicine>

DO NOT TAKE <medicine> - OR - TELL YOUR DOCTOR BEFORE TAKING <medicine>:

• If you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking isotretinoin.

Warnings and precautions - Take special care with <medicine>:

This medicine can cause serious skin reactions. Stop using <medicine> and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

Section 4

Stop using isotretinoin and seek medical attention immediately if you notice any of the following symptoms **of serious skin reactions**:

- reddish **non elevated, target-like or circular** patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome (SJS)/ toxic epidermal necrolysis (TEN)).

- **a red, scaly widespread rash with bumps under the skin and blisters accompanied by fever. The symptoms usually appear at the initiation of treatment [acute generalised exanthematous pustulosis (AGEP)]**

Gastrointestinal disorders, frequency "not known":

anal fissure (a small tear in the thin, moist tissue that lines the anus)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2025 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	25 January 2026
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 March 2026