

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:

The totality of data presented in this review suggest there is evidence that isotretinoin can be associated with sexual dysfunction including erectile dysfunction and decreased libido and that the mechanism may be a reduction in plasma testosterone.

Cumulatively total of 689 events occurring in 471 patients have been retrieved using the High Level Group Term 'Sexual function and fertility disorders'. The majority of cases reported erection and ejaculation conditions and disorders (311 cases), followed by High Level Term 'Sexual function and fertility disorders NEC' (165) and 'Spermatogenesis and semen disorders' (43). The most common Preferred Terms reported in these cases were: erectile dysfunction (281), libido decreased (92), sexual dysfunction (38), oligospermia (15), and ejaculation disorder (13). A negative dechallenge is reported in 10 cases and a positive dechallenge is reported in 15 cases. Two cases include rechallenge information: one negative and the other positive.

Based on the cases from spontaneous reporting and the literature review there is sufficient evidence to warrant an update to section 4.8 of the isotretinoin SmPC and the package leaflet.

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 4.8

The following adverse reactions should be added under the SOC "**Reproductive system and breast disorders**" in section 4.8 with a frequency "not known":

"Sexual dysfunction including erectile dysfunction and decreased libido"

Package Leaflet

4. Possible side effects

Unknown frequency: (frequency cannot be estimated from the available data)

- Dark or cola-coloured urine
- **Problems getting or maintaining an erection**
- **Lower libido**

Annex III

Timetable for the implementation of this position

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Adoption of CMDh position:	July 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	2 September 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	1 November 2017