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 clobetasol, the scientific conclusions are as follows:

In view of available data on misuse for a prolonged duration, necrotizing fasciitis, Kaposi's sarcoma and osteonecrosis 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 Lead Member State considers:

- that the risk of serious infections (including necrotizing fasciitis) and systemic immunosuppression (sometimes resulting in reversible Kaposi's sarcoma lesions) when combining clobetasol propionate with other medicines affecting the immune function should be documented in the warning section of the product information;
- that a causal relationship between clobetasol propionate and osteonecrosis is at least a reasonable possibility when clobetasol was used at doses or for duration beyond the ones recommended and that a warning on this AE deserves to be included in the product information;
- that misuse for a prolonged duration is frequent and problematic for clobetasol propionate, and that the (still valid) recommendations in the Posology section of the product information should be better highlighted, by a general bold/boxed warning at the beginning of the section.

The PRAC Lead Member State concluded that the product information 'SmPC sections 4.2 and 4.4 (and corresponding PL sections) of products containing clobetasol propionate 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 clobetasol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing clobetasol 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 clobetasol 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 4.2

The following warning should be included as bold and boxed text at the beginning of the section 4.2 of the SmPC. It summarizes information already outlined in the current section 4.2, but the goal is to highlight the core message on the recommended usage of clobetasol.

> **Clobetasol propionate belongs to the most potent class of topical corticosteroids (Group IV) and prolonged use may result in serious undesirable effects (see section 4.4). If treatment with a local corticosteroid is clinically justified beyond *[X]* weeks *[adapt to the maximum treatment duration recommended in the SmPC]*, a less potent corticosteroid preparation should be considered. Repeated but short courses of clobetasol propionate may be used to control exacerbations (see details below).**

- Section 4.4

A warning on osteonecrosis, serious infections and immunosuppression should be added as follows:

> **Cases of osteonecrosis serious infections (including necrotizing fasciitis) and systemic immunosuppression (sometimes resulting in reversible Kaposi's sarcoma lesions) have been reported with long-term use of clobetasol propionate beyond the recommended doses (see section 4.2). In some cases patients used concomitantly other potent oral/topical corticosteroids or immunosuppressors (e.g. methotrexate, mycophenolate mofetil). If treatment with local corticosteroids is clinically justified beyond *[X]* weeks *[adapt to the maximum treatment duration recommended in the SmPC]*, a less potent corticosteroid preparation should be considered.**

Package Leaflet

- Section 3 – How to use [tradename]

No corresponding change in the PL for the proposed modification of the SmPC section 4.2. The need to highlight the recommended posology is primarily intended to better alert the prescribers. Clobetasol propionate is not freely available in the EU.

- Addition in Section 2 - What you need to know before you use [tradename]

The following warnings should be added relating to osteonecrosis and serious infections/immunosuppression (necrotizing fasciitis and Kaposi's sarcoma):

Warning and precautions

Talk to your doctor or pharmacist before using [tradename] if:

[…]

- **you experience newly developed bone pain or worsening of previous bone symptoms during a treatment with *[tradename]*, especially if you have been using *[tradename]* for a prolonged time or repeatedly.**
- **you use other oral/topical medication containing corticosteroids or medication intended to control your immune system (e.g. for autoimmune disease or after a transplantation). Combining *[tradename] with* these medicines may result in serious infections.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	10/2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29/11/2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	20/01/2021