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 adapalene, the scientific conclusions are as follows:

The growing number of reports (i.e. n=1,590 during the reporting interval alone) of application site burn in combination with the available evidence obtained from seven spontaneous reports within EVDAS, are considered to substantiate a causal association between adapalene and application site burns. The proposal for an update is further substantiated given that the PT application site burn was also recommended to be included in the EU SmPCs for adapalene/benzoyl peroxide containing medicinal products following a PSUSA procedure for this combination of actives which concluded during the reporting interval for the current PSUR for adapalene. Overall, it is considered that there is sufficient evidence to warrant an update to section 4.8 of the SmPC with the PT application site burn. Corresponding updates should also be made to section 4 of the PIL.

During the reporting interval, Galderma closed a signal of pigmentation disorders and classified this particular safety topic as a potential risk not considered important. Considering the high volume of cases received by the MAH concerning skin discolouration in association with adapalene (n=1,462 cases cumulatively), in addition to further analysis of information from three spontaneous reports and the evidence presented within the study by Kang et al., it is considered that there is sufficient evidence from various data streams in combination with biological plausibility to warrant an update to section 4.8 of the SmPC and corresponding updates to section 4 of the PIL for adapalene in relation to pigmentation disorders (i.e. hypopigmentation, hyperpigmentation).

All index cases of application site burn reported events of second degree burn/chemical burn of the skin. Consequently, it is considered that the potential for severe burns, specifically second degree burns in association with adapalene, should be reflected within the product information.

Given the serious nature of the events of anaphylaxis and angioedema observed in association with adapalene, the plausible time to onset observed within the cases identified within EVDAS and the potential for systemic exposure in association with adapalene, it is considered that there is sufficient evidence to warrant an update to section 4.8 of the SmPC with corresponding updates to the PIL.

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 adapalene the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing adapalene 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 adapalene 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 reaction(s) should be added under the SOC Immune system disorders with a frequency of not known: **anaphylactic reaction, angioedema**;

The following adverse reaction(s) should be added under the SOC skin and subcutaneous tissue disorders with a frequency of not known: "**Application site burn", "skin hypopigmentation", skin hyperpigmentation"**

The following text should also be included in section 4.8:

Most of the cases of "application site burn" were superficial burns but cases with second degree burn reactions have been reported.

Package Leaflet

- Section 4

Contact a doctor right away if you notice any of the following symptoms-you may need urgent medical treatment: Swelling of the face, lips or throat which makes it difficult to swallow or breathe, rash, itching, hives and dizziness. This could be a sign of angioedema or a severe allergic reaction (frequency not known, cannot be estimated from the available data).

Not known (cannot be estimated from the available data)

- **Darkening of fair skin**
- **Lightening of darker skin**
- **Application site burn**

The following text should also be included in section 4:

Application site burns (mostly superficial burns but also second degree or severe burn) have been reported.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 May 2019
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 July 2019