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 sulfametrole / trimethoprim, sulfadiazine / trimethoprim, sulfamethoxazole / trimethoprim (co-trimoxazole), the scientific conclusions are as follows:

MAHs identified several literature reports of Sweet's syndrome following co-trimoxazole use. Aspen identified seven cases from the scientific literature. Confounding factors were present in two of these cases; in one case co-suspect drug was abacavir and rechallenge with co-trimoxazole was negative, and in the other the patient had a concurrent mesothelioma and was treated with other antibacterial agents, but dechallenge with co-trimoxazole was positive without corticosteroid treatment. Dechallenge was also positive in four other cases, while co-trimoxazole treatment was completed prior to the onset of the event in the remaining case. The temporal relationship was plausible in these cases and the role of co-trimoxazole in development of Sweet's syndrome could not be ruled out. Six additional cases of Sweet syndrome following co-trimoxazole treatment were identified by Embase search. MAH concluded that co-trimoxazole role in the reported events could not be excluded and proposed to update product information accordingly. These publications were also analysed by other MAHs. Chemidex and Rokitan had the same conclusion, and Teopharma stated that their SmPC had already been updated to add Sweet's syndrome as an adverse reaction (variation approved in 2015). Almirall, T&D Pharma and Roche did not propose any label updates. Roche concluded there was no evidence confirming the role of co-trimoxazole in causation of Sweet syndrome, although there were 13 cases (5 literature and 8 spontaneous) where causal association was deemed possible. According to the MAH's analysis diagnostic criteria for drug-induced Sweet's syndrome were met in only four literature reports. There were 11 additional reports (4 literature and 7 spontaneous) of Sweet's syndrome following co-trimoxazole use in Roche's safety database with possible alternative explanation and/or confounding factors.

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 sulfametrole / trimethoprim, sulfadiazine / trimethoprim, sulfamethoxazole / trimethoprim (co-trimoxazole) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing sulfametrole / trimethoprim, sulfadiazine / trimethoprim, sulfamethoxazole / trimethoprim (co-trimoxazole)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 sulfametrole / trimethoprim, sulfadiazine / trimethoprim, sulfamethoxazole / trimethoprim (co-trimoxazole)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

SOC Skin and subcutaneous tissue disorders

Frequency unknown: **Acute febrile neutrophilic dermatosis (Sweet's syndrome)**

Package Leaflet

- Section 4. Possible side effects

- plum-coloured, raised, painful sores on the limbs and sometimes on the face and neck with a fever (Sweets syndrome) (frequency unknown)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2019 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	26 January 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	26 March 2020