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 rabeprazole, the scientific conclusions are as follows:

The PRAC noted twenty reports provided by the MAH with events of microscopic colitis with the use of medicinal products of the same therapeutic class. Among these cases there were eight cases with positive de-challenge associated with rabeprazole use only and clearly support the association between rabeprazole treatment and the occurrence of microscopic colitis. Although according to data derived from an adverse event reporting system outside the EU, the overall number of reports of microscopic colitis for proton pump inhibitors is relatively small and the number of reports of microscopic colitis associated with rabeprazole is smaller compared to lansoprazole, these data should be viewed in the light of the fact that patient exposure is much higher for lansoprazole and that rarity of the disease difficult to diagnose (only via biopsy) suggests a significant under-reporting.

The PRAC also noted that a case-control study using the UK Clinical Practice Research Datalink including 1,211 cases, which supported an association of current use of proton pump inhibitors with an increased risk of microscopic colitis compared to no use and past use.

The PRAC also took into consideration the association of microscopic colitis and severe diarrhoea. Since diarrhoea is a common side-effect of many medications and elderly patients are more likely to take more medications, generally drug consumption is considered a contributing factor in the development of microscopic colitis, particularly in elderly patients.

Given the cases with positive de-challenge which clearly support the association between rabeprazole treatment and the occurrence of microscopic colitis, the relevance of severe diarrhoea especially in the elderly who are at increased risk for dehydration, the fact that of microscopic colitis is listed as adverse reaction in the class of products and finally the mechanism of action described in the scientific literature, the PRAC considered the causality established and recommended the update of the product information to include as adverse reaction microscopic colitis.

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 rabeprazole the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing rabeprazole 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 rabeprazole 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 system organ class gastrointestinal disorders with a frequency unknown:

microscopic colitis

Package Leaflet

Section 4 "Possible side effects"

inflammation of the gut (leading to diarrhoea)

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	June 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 August 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	4 October 2017