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 esomeprazole/naproxen, the scientific conclusions are as follows:

In view of available data on nephrotoxicity from the literature and as a class effect of proton pump inhibitors (PPIs), the PRAC considers a causal relationship between esomeprazole/naproxen and Tubulointerstitial nephritis (with possible progression to renal failure) is at least a reasonable possibility. The PRAC concluded that the product information of products containing esomeprazole/naproxen 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 esomeprazole/naproxen the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing esomeprazole/naproxen 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 esomeprazole/naproxen 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 4.4

A warning should be added as follows (exact wording):

Renal effects

Acute tubulointerstitial nephritis (TIN) has been observed in patients taking esomeprazole and naproxen containing products and may occur at any point during [Product name] therapy (see section 4.8). Acute tubulointerstitial nephritis can progress to renal failure.

[Product name] should be discontinued in case of suspected TIN, and appropriate treatment should be promptly initiated.

- Section 4.8 Naproxen

The following adverse reaction should be amended under SOC Renal and urinary disorders:

Tubulointerstitial nephritis **(with possible progression to renal failure)**

- Section 4.8 Esomeprazole

The following adverse reaction should be amended under SOC Renal and urinary disorders:

Tubulointerstitial nephritis **(with possible progression to renal failure)**

Package Leaflet

Under section "Warnings and precautions" the following should be added:

When taking [Product name], inflammation in your kidney may occur. Signs and symptoms may include decreased volume of urine or blood in your urine and/or hypersensitivity reactions such as fever, rash, and joint stiffness. You should report such signs to the treating physician.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	January 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	13 March 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 May 2023