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 nifuroxazide the scientific conclusions are as follows:

In view of available data on use during pregnancy and while breastfeeding, mutagenicity and carcinogenicity from in vitro/in vivo studies, the literature and spontaneous reports, the PRAC considers that nifuroxazide has showed possible mutagenic potential and therefore should not be used during pregnancy and while breastfeeding and should not be recommended for women of childbearing potential unless they are using an effective contraception. The PRAC concluded that the product information of products containing nifuroxazide 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 nifuroxazide the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing nifuroxazide 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 nifuroxazide 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 4.6

The recommendation regarding use in pregnancy, during breastfeeding and use in patients with childbearing potential should be amended or included as follows:

Pregnancy

There is limited amount of data from the use of nifuroxazide in pregnant women. Animal studies are insufficient with respect to reproductive toxicity. Nifuroxazide shows possible mutagenic potential (see section 5.3). Therefore, [product name] is not recommended during pregnancy and should not be used by women of childbearing potential who are not using effective contraception.

Lactation

It is not known if nifuroxazide or its metabolites are excreted into human breast milk. Because [product name] has poor bioavailability (absorption from GIT for about 10-20% of dose), the amount in the milk is likely to be low. However, an impact on breast fed infants gastrointestinal microbioma cannot be excluded. Due to lack of experience from clinical practice treatment with [product name] during breastfeeding is not recommended.

Fertility

No sufficient information on the effect of [product name] on fertility is available from animal studies.

- Section 5.2

Information regarding negligible (minimal) absorption from gastrointestinal tract should be deleted and replaced by the following information:

The product is partially absorbed (10-20%) from the gastrointestinal tract following peroral administration and is significantly metabolized, with the main moieties circulating in the blood being metabolites.

- Section 5.3

Information that data from genotoxicity and reproductive studies did not reveal any special risk to humans should be deleted. And the following information should be included in section 5.3:

Nifuroxazide shows possible mutagenic potential.

The carcinogenic potential of nifuroxazide was assessed in mice (50/gender/group) and rats (52/gender/group) who received nifuroxazide in diet for 2 years at doses 0, 200, 600

or 1800 mg/kg/day. Despite mutagenic properties, carcinogenicity of nifuroxazide has not been proven in mice nor in rats.

Based on surface area comparisons, the relative multiple of exposure to the maximum human dose of 1800 mg (493 mg/m2 assuming a 60 kg patient weight) of the 2-year mouse and rat studies (5400 mg/m2 and 10,800 mg/m2, respectively) is 11- and 22-fold.

Package Leaflet

2. What you need to know before you use [product name]

Warnings and precautions

- As a precaution, [product name] should not be given during pregnancy **and while breastfeeding**. ~~Use during breastfeeding is possible in case of short-term treatment.~~

Pregnancy and breast-feeding

As a precaution, [product name] should not be given during pregnancy **and while breastfeeding**. ~~Use during breastfeeding is possible in case of short-term treatment.~~ **In women of childbearing potential [product name] should only be used if they are using effective contraception.**

Timetable for the implementation of this position

Adoption of CMDh position:	April 2022 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	6 June 2022
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	5 August 2022