# 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 nitrofurantoin, nifurtoinol, the scientific conclusions are as follows:

Based on the review of literature and data from safety databases, the PRAC considered that a causal relationship between nitrofurantoin, nifurtoinol and autoimmune hepatitis, interstitial nephritis and cutaneous vasculitis is plausible and therefore recommends updating the Product Information by listing these adverse reactions with a frequency “unknown”. In addition, due to the seriousness of autoimmune hepatitis, this adverse drug reaction should also be reflected in section 4.4 of the Summary of Product Characteristics. The Package Leaflet should be updated accordingly.

Furthermore, based on the data provided by the Marketing Authorisation Holders and the literature data, the contraindication in patients with renal impairment is updated with regard to the level of estimated glomerular filtration rate (eGFR) cut-off to <45 ml/min.

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 nitrofurantoin, nifurtoinol the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing nitrofurantoin, nifurtoinolis 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 nitrofurantoin, nifurtoinol 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 4.3

*Contraindication pertaining renal impairment*

<…> (~~creatinine clearance below 60 ml/min~~)<…> (~~creatinine clearance below 40 ml/min~~) <…>

And delete any other values of creatinine clearance different of “below 45 ml/min”.

<…> (**eGFR below 45 ml/min**) <…>

Section 4.4

**Hepatotoxicity**

**Hepatic reactions, including hepatitis, autoimmune hepatitis, cholestatic jaundice, chronic active hepatitis, and hepatic necrosis, occur rarely. Fatalities have been reported. The onset of chronic active hepatitis may be insidious, and patients should be monitored periodically for changes in biochemical tests that would indicate liver injury. If hepatitis occurs, the drug should be withdrawn immediately and appropriate measures should be taken**.

Section 4.8

*Immune system disorders*: **Cutaneous vasculitis (frequency – unknown)**.

*Hepatobiliary disorders*: **Autoimmune hepatitis (frequency – unknown)**.

*Renal and urinary disorders:* **Interstitial nephritis (frequency – unknown).**

**Package Leaflet**

Section 2

**Warnings and precautions**

**Talk to your doctor if you experience fatigue, yellowing of the skin or eyes, itching, skin rashes, joint pain, abdominal discomfort, nausea, vomiting, loss of appetite, dark urine, and pale or gray-colored stools. It may be symptoms of liver disorder.**

Section 4

**Inflammation of small blood vessel walls, causing skin lesions with a frequency not known.**

**Liver inflammation due to turn of immune system against liver cells with a frequency not known.**

**Inflammation of kidney tissue surrounding tubules, causing renal impairment with a frequency not known.**

## Annex III

## Timetable for the implementation of this position

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|---|---|
| Adoption of CMDh position: | November 2018 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 03 January 2019 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 27 February 2019 |