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 gentamicin (systemic use), the scientific conclusions are as follows:

In view of available data on increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations from the literature and in view of a plausible mechanism of action, the PRAC considers that there is sufficient evidence to reflect a warning between gentamicin (systemic use) and increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations in the product information. The PRAC concluded that the product information of products containing gentamicin (systemic use) should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for gentamicin (systemic use) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing gentamicin (systemic use) is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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:

Ototoxicity

...

There is an increased risk of ototoxicity in patients with mitochondrial DNA mutations (particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene), even if aminoglycoside serum levels are within the recommended range during treatment. Alternative treatment options should be considered in such patients.

In patients with a maternal history of relevant mutations or aminoglycoside induced deafness, alternative treatments or genetic testing prior to administration should be considered.

Package Leaflet

- Section 2 subsection "Warnings and precautions"

Talk to your doctor before using <product name>

- if you have, or have a maternal history of mitochondrial mutation disease (a genetic condition) or loss of hearing due to antibiotic medicines, you are advised to inform your doctor or pharmacist before you take an aminoglycoside; certain mitochondrial mutations may increase your risk of hearing loss with this product. Your doctor may recommend genetic testing before administration of <product name>.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	December 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	28 January 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 March 2024