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 amikacin (except for centrally authorised products), the scientific conclusions are as follows:

In view of available data from the literature, the PRAC considers a causal relationship between amikacin and increased risk of aminoglycoside-associated ototoxicity in patients with mitochondrial mutations at least a reasonable possibility. The PRAC concluded that the product information of products containing amikacin 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 amikacin (except for centrally authorised products) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing amikacin (except for centrally authorised products) 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 amikacin (except for centrally authorised products) 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:

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 family 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 ...

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- if you or your family members have a 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>.

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:	12 March 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	11 May 2023