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

In view of available data from the literature describing the association between mitochondrial mutations and increased risk of ototoxicity, the PRAC considers a casual relation between mitochondrial DNA mutations, mainly m.1555A>G, and an increased risk of ototoxicity after aminogylcoside exposure is at least a reasonable possibility, also in patients who had aminoglycoside serum levels within the recommended ranges.
The PRAC concluded that the product information of products containing tobramycin for systemic use should be amended accordingly.

In view of the evidence, the PRAC considers that the risk of increased aminoglycoside ototoxicity due to mitochondrial DNA mutations is relevant also for the other systemic aminoglycoside, since it can be a class effect. The issue of increased aminoglycoside ototoxicity should be therefore revised in the next PSUSA procedures for all the systemic amyniglycosides and their FDC.

Update of section 4.4 of the SmPC to add a warning on the increased risk of ototoxicity in patients with mitochondrial DNA mutations. The Package leaflet is updated 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 tobramycin (systemic use) the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing tobramycin (systemic use) 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 tobramycin (systemic use) 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

(*Section to be implemented in the current subparagraph related to ototocicity already included in section 4.4 of tobramycin-containing products for systemic use*)

Patients with mitochondrial DNA mutations, particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene may be at higher risk for ototoxicity, even if the patient's aminoglycoside serum levels were within the recommended range. In case of family history of aminoglycoside-induced deafness or known mitochondrial DNA mutations in the 12S rRNA gene, alternative treatments other than aminoglycosides may need to be considered.

PIL
Section 2:
Warnings and precautions
Talk to your doctor before using Tobramycin

- if you or your family members have a mitochondrial mutation disease (condition caused by variants in the genome of mitochondria, the parts of your cells which help make energy) or loss of hearing due to antibiotic medicines; certain mitochondrial mutations may increase your risk of hearing loss with this product.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2021 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	5 July 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 September 2021