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 for the non-interventional imposed PASS final report for the medicinal product(s) containing the active substance teicoplanin and concerned by the PASS final report , the scientific conclusions are as follows:

The final study report submitted by the MAH complies with their obligation to conduct a prospective non-interventional post-authorisation safety study to further evaluate the incidence of nephrotoxicity and other adverse events of interest in patients treated with the higher recommended teicoplanin loading dose (12 mg/kg twice a day [BID]), and comparison with external historical comparator data as imposed during the Article 30 procedure EMEA/H/A-30/1301 for Targocid (teicoplanin).

The incidence of nephrotoxicity of 11.0% [7.4%; 15.5%] observed in the modified High-loading dose population confirmed by the ICAC during the loading dose analysis period (up to day 10) is significantly higher in comparison to the lower loading dose (about 2%) based on a metaanalysis of historical publications.

Therefore, in view of available data regarding the PASS final study report, the PRAC considered that changes to the product information and the conditions of the marketing authorisation were warranted.

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 the results of the study for the medicinal product(s) containing the active substance teicoplanin and concerned by the PASS final report , the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) mentioned above is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of the products concerned by this PASS final report 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 Summary of Product Characteristics (new text **underlined and in bold,** deleted text ~~strike through~~)

- Section 4.4

4.4 Special warnings and precautions for use

Teicoplanin should not be administered by intraventricular use.

…
~~Loading dose regimen~~
~~Since data on safety are limited, patients should be carefully monitored for adverse reactions when teicoplanin doses of 12 mg/kg body weight twice a day are administered.~~
~~Under this regimen blood creatinine values should be monitored in addition to the recommended periodic haematological examinations.~~

~~Teicoplanin should not be administered by intraventricular use.~~

Thrombocytopenia
Thrombocytopenia has been reported with teicoplanin **(see section 4.8)**. Periodic haematological examinations**, including complete blood count,** are recommended during treatment ~~including complete cell blood count~~.

Nephrotoxicity
Nephrotoxicity and r~~R~~enal failure ha**ve**~~s~~ been reported in patients treated with teicoplanin (see section 4.8). Patients with renal insufficiency, ~~and/or~~ in those receiving **the high loading dose regimen of teicoplanin, and those receiving** teicoplanin in conjunction with or sequentially with other medicinal products with known nephrotoxic potential (**e.g.** aminoglycosides, colistin, amphotericin B, ciclosporin, and cisplatin) should be carefully monitored, and should ~~include~~ **get** auditory tests **(see "Ototoxicity" below)**.

Ototoxicity
…
Patients receiving teicoplanin in conjunction with or sequentially with other medicinal products with known **nephrotoxic and/or** neurotoxic/ototoxic potential (**e.g.** aminoglycosides, **colistin, amphotericin B,** ciclosporin, cisplatin, furosemide and ethacrynic acid) should be carefully monitored and the benefit of teicoplanin evaluated if hearing deteriorates.
…

- Section 4.5

…
Teicoplanin should be used with care in conjunction with or sequentially with other medicinal products with known nephrotoxic **and/or neurotoxic**/ototoxic potential. These include **e.g.** aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide, and ethacrynic acid (see section 4.4 **"Nephrotoxicity" and "Ototoxicity").** However, there is no evidence of synergistic toxicity in combinations with teicoplanin.

- Section 4.8

Tabulated list of adverse reactions
In the table below all the adverse reactions, which occurred at an incidence greater than placebo and more than one patient are listed using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000
to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
~~Adverse reactions should be monitored when teicoplanin doses of 12 mg/kg body weight twice a day are administered (see section 4.4).~~

frequency 'Not known': Renal failure (including renal failure acute) **(see below description of selected adverse reactions)***

Investigations

~~Blood creatinine increase (transient rise of serum creatinine)~~

Description of selected adverse reactions

***Based on literature reports, the estimated rate of nephrotoxicity in patients receiving low loading dose regimen of average 6 mg/kg twice a day, followed by a maintenance dose of average 6 mg/kg once daily, is around 2%.**
In an observational post-authorisation safety study which enrolled 300 patients with a mean age of 63 years (treated for bone and joint infection, endocarditis or other severe infections) who received the high loading dose regimen of 12 mg/kg twice a day (receiving 5 loading doses as a median) followed by a maintenance dose of 12 mg/kg once daily, the observed rate of confirmed nephrotoxicity was 11.0% (95% CI = [7.4%; 15.5%]) over the first 10 days. The cumulative rate of nephrotoxicity from the start of treatment up to 60 days after the last dose was 20.6% (95% CI = [16.0%; 25.8%]). In patients receiving more than 5 high loading doses of 12 mg/kg twice a day, followed by a maintenance dose of 12 mg/kg once daily, the observed cumulative rate of nephrotoxicity from the start of treatment up to 60 days after the last administration was 27% (95% CI = [20.7%; 35.3%]) (see section 4.4).

Amendments to be included in the relevant sections of the Package Leaflet (new text **underlined and in bold,** deleted text ~~strike through~~)

2. What you need to know before you are given Targocid

…

Tests
During treatment you may have tests to check your blood, your kidneys**, your liver** and/or your hearing. This is more likely if:
☐ your treatment will last for a long time
☐ you need to be treated with high loading doses (12mg/kg twice a day)
☐ you have a kidney problem
…

4. Possible side effects

…
Tell your doctor or nurse straight away, if you notice any of the following serious side effects - you may need urgent medical treatment:

…

Not known (frequency cannot be estimated from the available data)
☐ lack of white blood cells – the signs may include: fever, severe chills, sore throat or mouth ulcers (agranulocytosis)
☐ kidney problems or changes in the way your kidneys work - shown in tests**. Frequency or severity of kidney problems may be increased if you receive higher doses.**
…

Annex III

Timetable for the implementation of this position>

Timetable for the implementation of the position

Adoption of CMDh position:	December 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	24 January 2021
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 March 2021