# 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 vancomycin, the scientific conclusions are as follows:

In view of available data on toxic epidermal necrolysis from spontaneous reports, including in some cases a close temporal relationship, a positive de-challenge and/or re-challenge, the PRAC considers a causal relationship between vancomycin and toxic epidermal necrolysis is at least a reasonable possibility. The PRAC concluded that the product information of products containing vancomycin should be amended accordingly.

Update of sections 4.4 and 4.8 of the SmPC to remove a warning on severe bullous reactions. to add a warning on severe cutaneous adverse reactions, to remove the adverse reaction "Lyell's syndrome" and to add the adverse reaction "toxic epidermal necrolysis" with a frequency of very rare. The Package leaflet is updated accordingly.

In view of available data on acute kidney injury due to interaction between vancomycin and piperacillin/tazobactam from the literature and spontaneous reports, the PRAC considers a causal relationship between vancomycin and acute kidney injury due to interaction between vancomycin and piperacillin/tazobactam is at least a reasonable possibility. The PRAC concluded that the product information of products containing vancomycin for parenteral use should be amended accordingly.

Update of sections 4.4 and 4.5 of the SmPC to add a warning on increased risk of acute kidney injury (AKI) with concomitant piperacillin/tazobactam treatment and the interaction. The Package leaflet is updated accordingly.

In view of available data on Haemorrhagic Occlusive Retinal Vasculitis (HORV) following intracameral or intravitreal administration from the literature, spontaneous reports and in view of a plausible mechanism of action for both administrations, the PRAC considers a causal relationship between vancomycin and Haemorrhagic Occlusive Retinal Vasculitis (HORV) following intracameral or intravitreal administration is at least a reasonable possibility. The PRAC concluded that the product information of products containing vancomycin for parenteral use should be amended accordingly.

Update of section 4.4 of the SmPC to add a warning on Haemorrhagic Occlusive Retinal Vasculitis (HORV) following intracameral or intravitreal administration. 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 vancomycin the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing vancomycin 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 vancomycin 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:

**Severe cutaneous adverse reactions (SCARs)**

**Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with vancomycin treatment (see section 4.8). Most of these reactions occurred within a few days and up to eight weeks after commencing treatment with vancomycin.**

**At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, vancomycin should be withdrawn immediately and an alternative treatment considered. If the patient has developed a SCAR with the use of vancomycin, treatment with vancomycin must not be restarted at any time.**

A warning should be removed as follows:

~~Severe bullous reactions~~

~~Stevens-Johnson syndrome (SJS) has been reported with the use of vancomycin (see section 4.8). If symptoms or signs of SJS (e.g. progressive skin rash often with blisters or mucosal lesions) are present, vancomycin treatment should be discontinued immediately and specialised dermatological assessment be sought.~~

A warning for parenteral formulations should be amended as follows:

Nephrotoxicity

Vancomycin should be used with care in patients with renal insufficiency, including anuria, as the possibility of developing toxic effects is much higher in the presence of prolonged high blood concentrations. The risk of toxicity is increased by high blood concentrations or prolonged therapy.

Regular monitoring of the blood levels of vancomycin is indicated in high dose therapy and longer-term use, particularly in patients with renal dysfunction or impaired faculty of hearing as well as in concurrent administration of nephrotoxic or ototoxic substances, respectively (see section**s** 4.2 **and 4.5**).

A warning for parenteral formulations should be added as follows:

**Eye disorders**

**Vancomycin is not authorized for intracameral or intravitreal use, including prophylaxis of endophthalmitis.**

**Hemorrhagic occlusive retinal vasculitis (HORV), including permanent loss of vision, have been observed in individual cases following intracameral or intravitreal use of vancomycin during or after cataract surgery.**

- Section 4.5

For parenteral formulations, "piperacillin/tazobactam" should be added as an example of nephrotoxic interaction, and "(see section 4.4)" should be added at the end of the nephrotoxic interaction description.

- Section 4.8

Summary of the safety profile

The following should be added:

**Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP) have been reported in association with vancomycin treatment (see section 4.4).**

Tabulated list of adverse reactions

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency very rare:

**Toxic epidermal necrolysis (TEN)**

The following adverse reaction(s) should be removed:

~~Lyell's syndrome~~

Description of selected adverse drug reactions

The following should be deleted:

~~If a bullous disorder is suspected, the drug should be discontinued and specialised dermatological assessment should be carried out.~~

**Package Leaflet**

Section 2 - What you need to know before you use vancomycin

Taking/using other medicines

Special care is needed if you are taking/using other medicines as some could interact with vancomycin, for example:

*For parenteral formulations only, "piperacillin/tazobactam" should be added to the active substances affecting the kidneys.*

Warnings and precautions

**Serious side effects that may lead to loss of vision have been reported following the injection of vancomycin in the eyes.** [parenteral formulations only]

Talk to your doctor or hospital pharmacist or nurse before using Vancomycin if:

- **You have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking vancomycin.**

**Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP) have been reported in association with vancomycin treatment. Stop using vancomycin and seek medical attention immediately if you notice any of the symptoms described in section 4.**

Section 4 – Possible side effects

**[start bold]Stop using vancomycin and seek medical attention immediately if you notice any of the following symptoms:[end bold]**

- **reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes. These serious skin rashes can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome and toxic epidermal necrolysis).**
- **Widespread rash, high body temperature and enlarged lymph nodes (DRESS syndrome or drug hypersensitivity syndrome).**
- **A red, scaly widespread rash with bumps under the skin and blisters accompanied by fever at the initiation of treatment (acute generalised exanthematous pustulosis).**

## Annex III

## Timetable for the implementation of this position

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| Adoption of CMDh position: | October / 2020 CMDh meeting |
| Transmission to National Competent Authorities of the translations of the annexes to the position: | 29 November 2020 |
| Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder): | 28 January 2021 |