# Annex II

## Scientific conclusions

**Scientific conclusions**

**Overall summary of the scientific evaluation of vancomycin-containing products** (see Annex I)

Vancomycin is a glycopeptide antibiotic authorised around six decades ago. Its effect is mainly bactericidal and it is exerted mainly by the inhibition of the cell wall peptidoglycan synthesis. Vancomycin spectrum includes a wide range of pathogens including *Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Streptococus pneumoniae*, *Listeria monocytogenes* and *Clostridium difficile*.

Vancomycin containing products are commercially available as:

- powder for solution for injection or infusion (500 mg and 1000 mg) used by intravenous administration. For certain medicinal vancomycin-containing products, the intraperitoneal route and oral route of administration are authorised,

- and capsules, for oral administration.

Vancomycin hydrochloride is defined as the hydrochloride salt of a mixture of related glycopeptides for which the characteristics are defined in the European Pharmacopeia 1058 monograph (currently under revision). The active substance is obtained mainly by fermentation.

The antibacterial activity of vancomycin is confined to Gram-positive microorganisms. Intravenous vancomycin is mainly used for the treatment of serious infections caused by microorganisms with mechanisms of resistance to beta-lactam antibiotics, in particular methicillin-resistant *Staphylococcus aureus* (MRSA), *coagulase-negative staphylococci* (CoNS) and *enterococci*, the latter being often tolerant to β-lactam antibiotics. It is also used in patients who are allergic to penicillins and cephalosporins. Vancomycin is also administered by the oral route for the treatment of *Clostridium difficile*-infection (CDI).

However, increases in the rates of heteroresistance and tolerance to vancomycin, combined with its pharmacodynamic (i.e. slow bactericidal activity, variable tissue penetration) and clinical (clinical failures reported in patients with invasive infections produced by *Staphylococcus aureus* with a MIC above 1 mcg/mL) shortcomings have questioned the current role of vancomycin for the treatment of these infections.

The emergence of multidrug-resistant pathogens is a growing problem worldwide. In view of the importance of ensuring the availability of efficacious antibiotics for the EU patients, in the interest of public health and in order to contribute to tackling the threat posed by the spread of antimicrobial resistance, a critical review of the benefit-risk of vancomycin containing products in the approved indications, including the relevant posology, was considered needed. In addition, significant differences between the product information of vancomycin-containing medicines across the EU Member States were identified in particular in the indications, posology and method of administration, but also in other sections of the product information. Therefore, in light of the above the Spanish Medicines Agency (AEMPS) considered in the interest of the Union to refer the matter to the CHMP and request that its gives its opinion under Article 31 of Directive 2001/83/EC on the benefit-risk of vancomycin-containing products and on the need for regulatory measures to be taken.

In its assessment, the CHMP reviewed all available data, including submissions by the marketing authorisation holders during the procedure and consulted the Paediatric Committee (PDCO), the CHMP relevant working parties/groups: Infectious Disease working party (IDWP), the Pharmacokinetics working party (PKWP), the Quality Working Party (QWP), the Modelling and Simulation Working Group (MSWG)) and external experts (the European Committee on Antimicrobial Susceptibility Testing (EUCAST)). Among other issues, the CHMP discussed the need for updating the wording of the product information.

Having reviewed all available data, and taking into account the current clinical practice and current clinical guideline recommendations, the CHMP considered that vancomycin is an important therapeutic option in the following indications:

- Treatment of: complicated skin and soft tissue infections, bone and joint infections, community acquired pneumonia, hospital acquired pneumonia including ventilator-associated pneumonia, infective endocarditis, bacteraemia that occurs in association with, or is suspected to be associated with any of the above (particularly those caused by *methicillin-resistant Staphylococcus aureus* (MRSA)), perioperative antibacterial prophylaxis. Current guidelines from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID[1,2]) and Infectious Diseases Society of America (IDSA[3]) also support its role in the treatment of MRSA infections.

- Treatment of acute bacterial meningitis. The CHMP noted that the current guidelines for the treatment of acute bacterial meningitis from several learned societies (ESCMID[4], IDSA[5] guideline and UK joint specialist societies guidelines[6], European Federation Neurological Societies (EFNS)) recommend vancomycin for both empirical treatment and etiological treatment of MRSA (alone) and penicillin-resistant *Streptococcus pneumoniae (*PRSP) in combination with other antibacterials in adults and children.

- Treatment of peritoneal dialysis–associated peritonitis. The CHMP noted the guidelines on the management of Peritoneal Dialysis-related peritonitis in adults from the International Society for Peritoneal Dialysis (ISPD) (Li PK et al., 2016[7]), the ISPD recommendations for pediatric patients (Warady BA et al., 2012[8]). In addition, the CHMP reviewed the available evidence submitted within the referral procedure including several references to published literature and a meta-analysis of a total of 64 studies (32 for initial treatment and negative culture, 28 reporting treatment for Gram-positive and 24 reporting treatment for Gram-negative) and 21 randomized clinical trials (14 for initial treatment and negative culture, 8 reporting treatment for Gram-positive and 8 reporting treatment for Gram-negative), confirming the efficacy of vancomycin for the treatment of peritonitis in peritoneal dialysis.

- Treatment of *Clostridium difficile* infection (CDI), for vancomycin given by oral route of administration. The CHMP noted that the European Society of Clinical Microbiology and Infection (ESCMID) issued a treatment guidance document[9,10] for *Clostridium difficile* infection in 2009 that is currently being updated. The guidance provides treatment recommendations for initial and recurrent CDI. In the case of mild CDI clearly induced by the use of antibiotics, it is acceptable to discontinue the inducing antibiotic and observe the clinical response. Vancomycin treatment is recommended in severe or recurrent cases. Currently, there is no evidence that medical prophylaxis for CDI is efficacious and therefore there is not recommended prophylactic antibiotics.

[1] ESCMID guidelines: https://www.escmid.org/escmid_publications/medical_guidelines/escmid_guidelines/
[2] ESCMID guideline
https://www.escmid.org/fileadmin/src/media/PDFs/4ESCMID_Library/2Medical_Guidelines/ESCMID_Guidelines/Eu_Rec_Antimicrobal.pdf
[3] IDSA guideline
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Antimicrobial_Agent_Use/Vancomycin/Vancomycin/
[4] Bacterial meningitis:ESCMID guideline for bacterial meningitis: http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(16)00020-3/abstract
[5] IDSA:
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organ_System/Central_Nervous_System_(CNS)/Bacterial_Meningitis/
[6] Joint guideline: https://www.britishinfection.org/files/5614/5674/2938/McGill_meningitis_guidelines_Final_published_proof.pdf
[7] PD-related peritonitis https://ispd.org/ispd-guidelines/
guidelines on the management of PD-related peritonitis in adults from the International Society for Peritoneal Dialysis (ISPD) (Li PK et al., 2016 http://www.pdiconnect.com/content/36/5/481.full
[8] ISPD recommendations for paediatric patients (Warady BA et al., 2012) - https://ispd.org/media/pdf/Consensus__Change_20_.pdf
[9]https://www.escmid.org/fileadmin/src/media/PDFs/4ESCMID_Library/2Medical_Guidelines/ESCMID_Guidelines/fulltext_treatment_guidance_Clostridium_difficile_infection.pdf
[10] Bauer MP. et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for *Clostridium difficile* infection (CDI). Clin Microbiol Infect 2009; 15: 1067–1079

The following indications of vancomycin (oral route) for "*treatment of staphylococcal enterocolitis"* and "*Decontamination of the gastrointestinal (GI) tract in immune-compromised patients when combined with an aminoglycoside*" were not supported by the CHMP:

- With regards to the "*treatment of staphylococcal enterocolitis",* the CHMP concluded that the MAHs did not provide data establishing the efficacy and safety of oral vancomycin in this indication. Furthermore, the CHMP noted that updated clinical guidelines for staphylococcal enterocolitis (diagnosis or treatment) do not mention this use of vancomycin. It is also noted that staphylococcal enterocolitis is a rare entity and that its diagnosis is controversial. Due to insufficient elements establishing the efficacy and safety of this the CHMP does not recommend this indication.
- Concerning the *"decontamination of the GI tract in immune-compromised patients when combined with an aminoglycoside",* the CHMP reviewed the available data submitted throughout this procedure. The data submitted in support of the vancomycin use for decontamination were not deemed as sufficiently robust. Furthermore, the role of selective intestinal decontamination is controversial. As a consequence, the CHMP is of the view that the benefit-risk for vancomycin containing products in the indication *"Decontamination of the gastrointestinal tract in immune-compromised patients when combined with an aminoglycoside"* is not established and therefore this indication is not recommended.

The CHMP also reviewed the dosage regimen for vancomycin for the various approved indications and patient subpopulations. The most commonly used dosage regimen (1 g every 12 hours) was considered adequate by the CHMP from a pharmacokinetic and pharmacodynamic perspective for the majority of patients with normal renal function and based on the usual susceptibility of staphylococci (minimum inhibitory concentration (MIC) ≤1 mg/L). However, the CHMP noted that the 2 g/day dose often results in $C_{trough}$ values below the target of 10 to 20 mg/l; therefore in order to achieve the optimal target concentration, the CHMP agreed that the vancomycin dose should be individually adapted according to weight, age and the underlying type and severity of infection and clinical response; the initial vancomycin doses should be calculated based on the body weight.

The CHMP acknowledged that the current therapeutic guidelines stress the importance of therapeutic drug monitoring and the use of the trough vancomycin concentration as a surrogate for the target AUC. The CHMP noted that the measurement of trough serum concentrations at steady state is an accepted surrogate to check if effective vancomycin exposure has been achieved. However, having reviewed the data presented by the MAHs, the CHMP also considered the existing limitations of monitoring $C_{trough}$ in certain situations. Trough-only monitoring may be not sufficient to guide vancomycin dosing in all cases, because peak levels (Cmax) are primarily influenced by the volume of distribution. Therefore, the CHMP discussed different alternative approaches to estimate the vancomycin exposure.

Overall, the CHMP considered that, out of the discussed methods, the Bayesian interpolation seemed to be an appropriate alternative; it allows predicting many individual pharmacokinetic parameters for extrapolation, minimizes the number of measurements on a single patient and seems to develop optimal strategies for therapeutic intervention. In addition, in line with the outcome of the MSWG consultation, the CHMP concluded that Bayesian methods could be clinically useful for more accurate dose predictions as a complementary part of routine therapeutic drug monitoring (TDM), especially for the patient groups with altered pharmacokinetic (PK) profile (i.e. children, haemodynamically unstable patients, intensive care), and acknowledged that this is already in clinical use. The wording on therapeutic drug monitoring in section 4.2 of the SmPC has been amended accordingly by the CHMP. It is currently made clear that TDM frequency needs to be individualised based on the clinical situation and response to treatment; specific recommendations are made for hemodynamically stable and

unstable patients, patients with normal renal function and patients on intermittent haemodialysis. The potential usefulness of model-based methods in the prediction of individual dose requirements to reach an adequate AUC is also addressed. A statement in the section 4.2 had been included accordingly by the CHMP.

The CHMP also reviewed the dose recommendation in paediatric population. For both infants, children aged from one month to 18 years old, the CHMP agreed that, as for adults, the vancomycin dose should be individually adapted according to weight, age and the underlying type and severity of infection and clinical response; the initial vancomycin doses should be calculated based on the body weight. The CHMP also acknowledged that some already approved vancomycin containing medicines already include some dosing recommendations for both term and preterm neonates[11]. For this specific group, the PDCO recommended one possible dosing regimen based on post-menstrual age (similar to the recommended dosing regimen by the British National Formulary (BNF) for children), but overall CHMP agreed that no universal recommendations on the dosage regimen in neonates could be made and that for establishing the dosing regimen in this population, the advice of a physician experienced in the management of neonates should be sought. The SmPC has been amended accordingly, including the dosing regimen in children based on post-menstrual age as a possible way of dosing vancomycin in this population.

Regarding the administration of vancomycin as a continuous infusion in paediatric patients, PDCO confirmed that it is being used in some countries for neonates (and children) with severe infections such as patients with central nervous system infections and/or associated bacteremia. In these cases, continuous infusions were used due to a failure of response to treatment or to a persistence of sub-therapeutic vancomycin levels despite optimizing dosing and frequency during intermittent vancomycin administration. However, continuous vancomycin infusions have a few disadvantages such as that there may be compatibility issues with other IV medications or solutions that are given concurrently; practical problems associated with reduced line availability when infusions are given over a 24-h period; increased risk of infusing a bolus dose of vancomycin when the intravenous solution is changed or when another medication is infused into the same intravenous tubing which is filled with vancomycin 24 h/day etc. Moreover, existing data (including comparative) on the use of a continuous vs. an intermittent infusion are not conclusive.

As a consequence, the CHMP could not recommend any concrete dosing recommendations for continuous infusion in the SmPC of vancomycin for IV use.

The CHMP reviewed also the optimal way of expressing the strength and dose of vancomycin-containing products. CHMP was of the opinion that, given the fact that the use of milligram to prescribe this product was established in EU clinical practice, it is essential that the convention of labelling vancomycin products by mass, i.e. milligrams, is retained. However, to ensure that the established therapeutic dose in terms of IU (potency) is maintained, and as indicated in the Question and Answer on expression/declaration of potency in quantitative and qualitative composition for vancomycin products (EMA/CHMP/QWP/667469/2015), the amount (mg) of active substance in the drug product should be adjusted to achieve the declared product strength in terms of IU. The CHMP also reviewed the limits for related substances and impurities in the active substance and in the finished products and it was concluded that the limits for related components and impurities in the drug substance and in the final drug products already authorised are qualified. The Annex 3 of the CHMP guideline on setting specifications for related impurities in antibiotics would apply to new active substances and for new sources of existing active substances. Once vancomycin monograph in the Ph.Eur. will enter into force, the limits of the impurities in the drug substance and final drug products will need to be revised accordingly, where applicable.

[11] http://www.medicines.org.uk/emc/medicine/20836

The CHMP also reviewed the existing data on adverse reactions observed with the use of vancomycin and which confirm that the use of vancomycin for parenteral use is associated with nephrotoxicity and ototoxicity, infusion related adverse reactions like vein and tissue toxicity as well as hypersensitivity reactions. CHMP agreed that these risks can be minimised by appropriate warnings and recommendations in the product information.

Finally, revisions were made to sections 5.1 and 5.2 to reflect current pharmacokinetic and pharmacodynamic data, and to sections 1 and 2 to reflect the amount of active substance in the finished product (based on the potency expressed in IU), and the dose and strength of vancomycin containing products (to be expressed in milligrams). The CHMP noted that no update of the EUCAST breakpoints is warranted at this time.

In conclusion, the CHMP is of the opinion that the benefit-risk balance of the vancomycin-containing products included in the scope of this procedure remains positive under normal conditions of use, taking into account the agreed changes to the product information as set out in Annex III to the opinion.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for vancomycin-containing products.

**Grounds for the variation to the terms of the marketing authorisation, as applicable**

Whereas,

- Vancomycin-containing medicinal products has an increasingly important role in the treatment of Gram-positive bacterial infections,
- the existing product information including the indications, dosage recommendations and pharmacokinetic and pharmacodynamic information for vancomycin-containing products in the EU need to be revised in accordance with the latest available information,
- the CHMP carried out a benefit-risk evaluation of vancomycin containing products under Article 31 of Directive 2001/83/EC, reviewing all available data, including responses submitted by the marketing authorisation holders during the procedure and recommendations from the Paediatric Committee (PDCO), the CHMP relevant working parties/groups: Infectious Disease working party (IDWP), the Pharmacokinetics working party (PKWP), the Quality Working Party (QWP), the Modelling and Simulation Working Group (MSWG)) and external experts (the European Committee on Antimicrobial Susceptibility Testing (EUCAST),
- the CHMP considered that vancomycin represent a crucial therapeutic option in the context of the treatment of serious infections (complicated skin and soft tissue infections, bone and joint infections, community acquired pneumonia, hospital acquired pneumonia including ventilator-associated pneumonia, infective endocarditis, acute bacterial meningitis, bacteraemia that occurs in association with, or is suspected to be associated with, any of the above, perioperative antibacterial prophylaxis, peritoneal dialysis–associated peritonitis and treatment of *Clostridium difficile* infection) caused by Gram-positive pathogens, particularly those caused by MRSA,
- the CHMP considered the available data to be sufficient to support revisions of the indication for both oral use and parenteral use, as well as the posology in adults and paediatrics populations, in line with clinical experience and current therapeutic guidelines,
- the CHMP considered that the risks of nephrotoxicity, ototoxicity, infusion related adverse reactions and hypersensitivity reactions observed with vancomycin for intravenous use can be minimised by appropriate warnings and recommendations in the product information,
- the CHMP considered that the pharmacokinetic and pharmacodynamic data in the product information need to be updated,
- the CHMP considered that the amount of active substance in the finished product is determined and consistently based on the potency expressed in IU, and that the dose and strength of vancomycin containing products should continue to be expressed in milligrams,

The Committee, as a consequence, concluded that the benefit-risk balance of the vancomycin containing products included in the scope of this procedure remains positive under normal conditions of use, taking into account the agreed changes to the product information.