18 May 2017
EMA/645288/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Referral under Article 31 of Directive 2001/83/EC

Vancomycin containing medicinal products

Procedure number(s): EMEA/H/A-31/1440

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Information on the procedure

1.1. Referral of the matter to the CHMP

Vancomycin is an important therapeutic option to treat serious infections caused by a group of bacteria known as Gram-positive organisms. Because of a growing problem of infections that are resistant to multiple antibiotics including vancomycin, it is considered of high relevance that the way this antibiotic is used in treating infections is re-assessed and that the product information for vancomycin-containing products is updated in light of available data.

As part of the EU strategy to update the product information of older antibacterial agents in the context of the fight against antimicrobial resistance, on 21 March 2016, the Spanish Competent Authority (AEMPS) initiated a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the benefit-risk balance of vancomycin containing medicinal products and on the need of regulatory measures to be taken.

2. Scientific discussion

2.1. Introduction

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.

2.2. Quality

2.2.1. Expression of amount of active substance in the finished product and Expression of the strength

According to the revised Questions & Answers (Q&A) from the QWP on expression/declaration of potency in quantitative and qualitative composition for vancomycin products (EMA/CHMP/QWP/128067/2014), it should be ensured that amounts of active substance in the finished product is determined and consistently based on the potency expressed in IU.

In order to avoid confusion in clinical practice, the conventional labelling of vancomycin by ‘mg’ strength is to be maintained. However, the vial/capsule content should be adjusted to achieve the declared product strength in terms of IU.

The product information should therefore declare the qualitative and quantitative details of the active substance in terms of mass and IU, taking into account the Ph. Eur. minimum potency requirements. The manufacturing process and batch formulae should be revised where necessary, to achieve the declared content e.g. 500,000 IU or 1,000,000 IU.

To take account of the convention used for vancomycin products, the product information should be expressed as follows:

> Vancomycin 500 mg powder for concentrate for solution for infusion:
> Each vial contains 500 mg vancomycin hydrochloride equivalent to 500,000 IU vancomycin.
>
> Vancomycin 1000 mg powder for concentrate for solution for infusion:
> Each vial contains 1000 mg vancomycin hydrochloride equivalent to 1,000,000 IU vancomycin.
>
> Vancomycin 125 mg capsule:
> Each capsule contains 125 mg vancomycin hydrochloride equivalent to 125,000 IU vancomycin.

Vancomycin 250 mg capsule:
Each capsule contains 250 mg vancomycin hydrochloride equivalent to 250,000 IU vancomycin.

2.2.2. Limits for related substances in the active substance and finished product specifications

Following consultation with the QWP, it was concluded that:

- The scope of the CHMP "Guideline on setting specifications for related impurities in antibiotics" applies to new active substances and for new sources of existing active substances.
- Since the referral refers to active substance and finished products already marketed in EU, the impurities on those products are considered qualified. However, for new sources the limits in the guideline (namely, identification and qualification thresholds: 0.15%) would apply.
- Finally, it was noted that the Ph. Eur monograph for vancomycin is under revision.

2.3. Clinical aspects

2.3.1. Efficacy

The MAHs were requested to provide information and supportive data on currently approved indications, posology and method of administration, special warnings and precautions, undesirable effects, pharmacodynamic properties and pharmacokinetic properties.

2.3.1.1. Overview of the indications and posology at the start of the procedure

The ***indications*** reflected in the SmPC for vancomycin-containing products vary across the Member States. They are summarised as follows:

- Intravenous vancomycin should only be used in patients who cannot be treated with or failed to respond or are resistant to other antibiotics such as penicillins and cephalosporins.
- The therapeutic use of vancomycin was restricted to only severe infection (targeted to potentially life-threatening infections, severe staphylococcal infections, severe infections caused by caused by gram-positive bacteria, etc.).
- Same therapeutic indications were considered for adults and paediatric population.
- Overall, most of the SmPCs included the following infections caused by gram-positive bacteria susceptible to vancomycin:
    1. complicated skin and soft tissue infections (with some wordings more restricted or qualified than others),
    2. bone and joint infections (some of them specifically mentioning osteomyelitis),
    3. community acquired pneumonia (only pneumonia is mentioned in some of the SPC submitted),
    4. hospital acquired pneumonia (not in all SPCs),

5. endocarditis (named infective endocarditis, endocarditis or pathogen specific endocarditis).

- The following indications were included in a few SmPCs:

    1. prophylaxis against endocarditis (the possible use of vancomycin as a perioperative or dental prophylaxis against bacterial endocarditis in patients at risk is not included in all SPC),
    2. Bacteraemia or sepsis,
    3. Oral use in the treatment of *Clostridium difficile* infection or the use in *staphylococcal enterocolitis* for the intravenous presentation,
    4. Peritonitis caused by *Staphylococcus aureus* or *Staphylococcus epidermidis* in dialysis patients,
    5. CNS infections.

- Few SmPCs propose combination with other antibacterial agents, where appropriate as a general recommendation or propose specific combinations with other antibiotic, e.g. in endocarditis.

With regards to the posology, several differences concerning the ***posology and the method of administration*** have been identified. The below recommendations are included in some SmPCs only:

- General recommendation stating that the dose should be individually adapted according to weight, age and the underlying type and severity of infection and clinical response,
- Loading dose in infants and newborn (with slight differences for loading dose and maintaining dose),
- Body weight dosing regimen in adults,
- Specific dosage recommendations for prophylaxis use,
- Information concerning adolescents, older people and obese patients,
- Nomogram for precise adjustment dose for patients with impaired renal function and formula for dose calculation, or adjustment of dose in a tabulated format,
- Creatinine clearance and alternate dose calculation,
- Recommendations about monitoring serum concentration of vancomycin,
- Pregnancy section,
- Inconsistent recommendations for patients with impaired liver function (precautions to apply in patients with severely impaired liver function, or no evidence that a dosage reduction is required in patients with impaired liver function).
- Recommendations for impaired kidney function,
- Statement with regards to concentrations of solutions for the patients requiring fluid restriction.

2.3.1.2. Indications and posology

The CHMP noted that Vancomycin is authorised as first line treatment for infections caused by methicillin-resistant staphylococci. Current therapeutic guidelines from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Infectious Diseases Society of America (IDSA) confirm its role in the treatment of MRSA infections.

Based on the data submitted by the MAHs during the procedure (i.e. clinical data including pivotal trials, publications and summaries of the indications and posology sections of their SmPCs) and having considered the current clinical guidelines and clinical practice, the CHMP confirms that the following indications are supported for the following formulations:

- For the powder for concentrate for solution for infusion
    1. Treatment of complicated skin and soft tissue infections,
    2. Treatment of bone and joint infections,
    3. Treatment of community acquired pneumonia,
    4. Treatment of hospital acquired pneumonia, including ventilator-associated pneumonia,
    5. Treatment of infective endocarditis.
- For the Oral Use:

  Vancomycin capsules are indicated in patients 12 years and older for the treatment of *Clostridium difficile* infection (CDI).

However, the CHMP questioned some indications (and related posology) and requested additional information to the MAHs:

- Infective endocarditis,
- endocarditis prophylaxis (perioperative or dental prophylaxis against bacterial endocarditis in patients at risk),
- peritonitis in dialysis patients caused by S aureus or S epidermidis,
- bacteraemia in relation to the infections mentioned,
- CNS infections,
- Specific combinations with other antibacterial agents by indications.

- *Infective endocarditis and perioperative prophylaxis against bacterial endocarditis*

The MAHs were requested to discuss if weight-based dosing should also be used in the treatment of endocarditis and to clarify (1) if the dosing should be based on actual body weight or lean body weight, and (2) the maximum dose in adults. The MAHs were also requested to further discuss if a dosage recommendation for children should be added to the indication *"perioperative prophylaxis against bacterial endocarditis".*

Studies investigating dosing of vancomycin for perioperative prophylaxis against bacterial endocarditis for children are not available to date; the MAHs focused their review on bacterial endocarditis treatment regimen. Based on clinical practice, antibiotic doses for children have been extrapolated from adult studies and are also supported by therapeutic guidelines for the prevention of bacterial

endocarditis[1]. Several MAHs' recommendations are also supported by the IDSA guidelines (clinical practice guidelines for antimicrobial prophylaxis in surgery) where the recommended prophylactic dose of vancomycin for both adult and paediatric patients is 15 mg/kg.

Based on the above, the CHMP endorses the indication and the posology for perioperative antibacterial prophylaxis in patients that are at high risk of developing bacterial endocarditis when undergoing major surgical procedures in all age groups and reflects this accordingly in the sections 4.1 and 4.2 of the SmPC.

- *"Bacteraemia in relation to the infections mentioned" (intravenous administration)*

This indication was not present in all SmPCs. The *MRSA* strains with higher vancomycin minimum inhibitory concentration (MIC) values are predictive of increased treatment failure (30-day mortality) and longer duration of bacteraemia in patients receiving vancomycin therapy. The CHMP reviewed the overall benefit of vancomycin based on the type of infection and for bacteria with MIC breakpoint >1 mg/l. EUCAST also discussed the issue and concluded that it is not warranted changing the vancomycin breakpoints for *Staphylococcus spp*. at this time.

The CHMP concluded that the evidence of an association between higher vancomycin MICs within the wild-type population and outcome of treatment with vancomycin is conflicting; the interpretation of the different studies is further confounded by the use of different technologies to determine the vancomycin MIC, and conventional adult doses frequently result in suboptimal exposure even in patients infected with strains with a vancomycin MIC of 1 µg/mL.

Based on the above, the CHMP endorses the indication of "bacteraemia that occurs in association with, or is suspected to be associated with, any of the above" and reflects this accordingly in the section 4.1 of the SmPC.

- *CNS infections (intravenous administration)*

With regard to *acute bacterial meningitis (ABM)*, the MAHs discussed the clinical experience of vancomycin in the treatment of ABM in adults and in children (including updated review of scientific literature and therapeutic guidelines), with a particular analysis on posology, scheme of administration especially regarding management of infection due to *Streptococcus pneumoniae* according to the degree of susceptibility to cephalosporins.

All MAHs' answers refer to current recommendations for the treatment of acute bacterial meningitis from several learned societies (ESCMID, IDSA guideline and UK joint specialist societies guidelines, European Federation Neurological Societies (EFNS)) where vancomycin is recommended for both empirical treatment and definitive treatment of MRSA (alone) and *penicillin-resistant Streptococcus pneumoniae (*PRSP) (in combination with other antibacterials) in adults and children.

There are some discrepancies regarding management of infection due to *Streptococcus pneumoniae* according to the degree of susceptibility to cephalosporins. The ESCMID guideline on "diagnosis and treatment of acute bacterial meningitis"[2] as well as publications (van de Beek D et al., 2006[3]; Suntur BM et al., 2005[4]; Lee H. et al., 2004[5]; Friedland IR et al.[6], 1993; Karageorgopoulos DE et al.2009[7])

1 AHA Scientific Statement - Infective Endocarditis in Childhood: 2015 Update, A Scientific Statement from the American Heart Association: http://circ.ahajournals.org/content/132/15/1487
2 ESCMID guideline: http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(16)00020-3/fulltext
3 van de Beek D, de Gans J, Tunkel AR, Wijdicks EF. Community-acquired bacterial meningitis in adults. N Engl J Med 2006;354:44–53
4 Suntur BM, Yurtseven T, Sipahi OR, Buke C, Buke M. Rifampicin + ceftriaxone versus vancomycin + ceftriaxone in the treatment of penicillin- and cephalosporin-resistant pneumococcal meningitis in an experimental rabbit model. Int J Antimicrob Agents 2005;26: 258–60
5 Lee H, Song JH, Kim SW, Oh WS, Jung SI, Kiem S, et al. Evaluation of a triple-drug combination for treatment of experimental multidrugresistant pneumococcal meningitis. Int J Antimicrob Agents 2004;23:307–10
6 Friedland IR, Paris M, Ehrett S, Hickey S, Olsen K, McCracken Jr GH. Evaluation of antimicrobial regimens for treatment of experimental penicillin- and cephalosporin-resistant pneumococcal meningitis. Antimicrob Agents Chemother 1993;37:1630–6
7 Karageorgopoulos DE, Valkimadi PE, Kapaskelis A, Rafailidis PI, Falagas ME. Short versus long duration of antibiotic therapy for bacterial meningitis: a meta-analysis of randomised controlled trials in children. Arch Dis Child 2009;94:607–14

recommend vancomycin when there is a risk of decreased susceptibility of *S. pneumoniae*, but mentioning that ceftriaxone or cefotaxime may be used as empiric treatment instead of vancomycin or rifampicin when true resistance to third-generation cephalosporin (minimum inhibitory concentration (MIC) >2 mg/L) is not to be expected. However, IDSA and UK guidelines set at cefotaxime/ceftriaxone MIC >0.5 µg/mL (which includes intermediate susceptibility) and EFNS, does not mention specific MIC.

Concerning dosing recommendation, there is no consensus although IDSA, ESCMID and EFNS give similar recommendations (up to 60 mg/kg/day for both adults and children) differing mainly in the lower level of dosing recommendation.

Overall, based on the above, the CHMP is of the view that vancomycin can be used in the treatment of *"acute bacterial meningitis"* (intravenous administration). The posology has been updated in adult and paediatric populations, which is also in accordance with the ESCMID guideline recommendations. Where appropriate, vancomycin should be administered in combination with other antibacterial agents.

- *Peritonitis caused by Staphylococcus aureus or Staphylococcus epidermidis in dialysis patients (intraperitoneal administration)*

This indication is not reflected in all SmPCs. MAHs referred in their responses to the recommendations of the guidelines on the management of PD-related peritonitis in adults from the International Society for Peritoneal Dialysis (ISPD) (Li PK et al., 2016[8]) and the ISPD recommendations for paediatric patients (Warady BA et al., 2012[9]). One MAH has summarized the available evidence with several references to published literature and including 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).

Overall, it is recommended that empirical antibiotic regimens should cover both gram-positive and gram-negative organisms. The combination of a glycopeptide (vancomycin or teicoplanin) plus ceftazidime was considered to be superior to other regimens in a proportional meta-analysis. In addition, several studies compared a first-generation cephalosporin with a glycopeptide-based regimen. Depending on the cephalosporin doses used, the conclusions vary, but overall, the CHMP noted no significant difference in the complete cure rate, rate of primary treatment failure, relapse, or catheter removal. Due to a high rate of methicillin-resistant organisms, vancomycin may be preferable for empirical gram-positive coverage. The CHMP reviewed these data and concluded the efficacy of vancomycin in the "*treatment of peritoneal dialysis–associated peritonitis*" indication. The posology has been updated, following the dosing recommendations stated in the ISPD guidelines.

The CHMP noted that this indication is recommended by consensus guideline as well as published literature confirming the efficacy of vancomycin for the treatment of peritonitis in peritoneal dialysis.

- *Specific combinations with other antibacterial agents by indications*

There are indications where combination therapy of i.v. vancomycin with other antibiotics is recommended (particularly endocarditis).

The CHMP discussed amendments to this wording and appropriate section of the SmPC for its inclusion. The CHMP concluded that the sentence *"Consideration should be given to official guidance on the appropriate use of antibacterial agents"* should be inserted in the section 4.1 of the SmPC, with a general reference in the section 4.2 to direct prescribers to take note of any existing national or local guidance and opinions on how vancomycin should be used and which combinations are recommended.

8 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
9 ISPD recommendations for paediatric patients (Warady BA et al., 2012) - https://ispd.org/media/pdf/Consensus__Change_20_.pdf

- *Clostridium difficile infection (CDI) (oral administration)*

The main manifestation of the CDI is the *Clostridium difficile*-associated diarrhoea (CDAD). The CDAD results from overgrowth in the colon of toxin-producing strains of *Clostridium difficile*, a Gram-positive, anaerobic, spore-forming bacterium. CDAD includes a wide spectrum of clinical presentations ranging from diarrhoea to fulminant, and/or fatal colitis (Dallal RM et al., 2002[10]). Prompt and precise diagnosis is therefore an important aspect of effective management of patients with CDAD. Laboratory analysis of stool samples to confirm the presence of *Clostridium difficile* and the presence of its toxins is the standard diagnostic test for CDAD.

Major changes in the epidemiology of *Clostridium difficile* infection have occurred since the emergence of the epidemic hypervirulent BI/NAP1/ribotype 027 strain in the late 1990s–early 2000s. With the emergence of this strain, a dramatic increase in the incidence of CDI has occurred worldwide with increasing numbers of infections reported in the community setting, and in previously thought low-risk populations such as healthy individuals without recent antibiotic exposure, and children (Cohen MB, 2010[11]).

The European Society of Clinical Microbiology and Infection (ESCMID) issued a treatment guidance document for *Clostridium difficile* infection in 2009 that is currently being updated (Bauer MP. et al. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for CDI. Clin Microbiol Infect 2009; 15: 1067–1079). The update is mainly intended to provide an overview of currently available CDI treatment options as well as develop an evidence-based update of treatment recommendations (Debast SB et al, 2014[12]). An episode of CDI is defined as: "A clinical picture compatible with CDI and microbiological evidence of free toxins and the presence of C. difficile in stool without reasonable evidence of another cause of diarrhoea." or "Pseudomembranous colitis as diagnosed during endoscopy, after colectomy or on autopsy".

Recurrence is present when CDI re-occurs within 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved after completion of initial treatment. It is not feasible to distinguish recurrence due to relapse (renewed symptoms from already present CDI) from recurrence due to reinfection in daily practice.

Severe CDI is defined as an episode of CDI with (one or more specific signs and symptoms of) severe colitis or a complicated course of disease, with significant systemic toxin effects and shock, resulting in need for ICU admission, colectomy or death. Clostridium difficile infection without signs of severe colitis in patients with greater age (≥65 years), serious comorbidity, Intensive Care Unit (ICU) admission, or immunodeficiency may also be considered at increased risk of severe CDI.

The indication for CDI covers children down to birth whilst acknowledging that in infants below 1 year of age with diarrhoea the diagnosis of CDAD is difficult and associated with a high risk of false positives due to the high (up to 70%) asymptomatic colonisation rate with *Clostridium difficile* and the high prevalence of other GI pathogens (e.g., rotavirus) causing diarrhoea in these infants. Neonates represent a group previously thought to be unaffected by C. difficile. However, Benson et al (2007[13]) in a retrospective study found that in the neonatal intensive care unit, C. difficile toxin was detected in stool specimens collected from 22 patients aged from 15 days to 6 months. A review of these patients' medical records revealed that 20 (91%) of these patients demonstrated underlying gastrointestinal

10 Dallal, R. M., Harbrecht, B. G., Boujoukas, A. J., Sirio, C. A., Farkas, L. M., Lee, K. K., & Simmons, R. L. (2002). Fulminant Clostridium difficile: an underappreciated and increasing cause of death and complications. Annals of surgery, 235(3), 363-372.
11 Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America.; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31(5):431-55
12 Debast SB, Bauer MP and Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: Update of the Treatment Guidance Document for Clostridium difficile Infection. Clin Microbiol Infect 2014; 20 (Suppl. 2): 1–26
13 Benson L, Song X, Campos J, Singh N. Changing epidemiology of Clostridium difficile-associated disease in children. Infect Control Hosp Epidemiol. 2007;28(11):1233-5

pathology, 5 (23%) underwent small bowel resection, and another 5 (23%) received a diagnosis of colitis. Four of these patients (18%) underwent colostomy or colectomy, and 11 (50%) had suspected or confirmed necrotizing enterocolitis. The authors concluded that it is necessary to reassess the role of this pathogen in the neonate as CDI in neonates may be more frequent than has so far been assumed. Furthermore, is current practice that if CDI is suspected in very young children they are treated with the same therapies as adult patients.

Therefore, taking into account the clinical data submitted by the MAHs, the CHMP is of the view that the use of oral vancomycin should be reflected as follows in in section 4.1 of the SmPC:

"Vancomycin is indicated in all age groups for the treatment of Clostridium difficile infection (CDI) (see sections 4.2, 4.4 and 5.1)". Cross-reference should be made not only to section 5.1 but also to section 4.4 in which caution is advised in relation to the potential to reach clinically significant systemic concentrations after oral administration, e.g. in patients with severe disease or after high oral doses of oral vancomycin.

The CHMP requested the MAHs to discuss the appropriate dosing recommendations for vancomycin when used orally for the treatment of CDI:

- In relation to the posology intended for the treatment of CDI, the standard vancomycin oral dose for adult patients with non-severe disease recommended in the ESCMID guideline (Debast SB et al, 2014[12]) is 125 mg four times daily for a period of 10 days.
- Currently, two dosing regimens for multiple recurrences of CDI are discussed and recommended in the ESCMID guideline (Update of the treatment guidance document for Clostridium Difficile infection; Debast SB et al, 2014[12]). This guideline also includes recommendations for situations when no oral treatment is possible. The inclusion of the ESCMID guideline recommendations in section 4.2 of the SmPC was discussed and agreed with the MAHs.

The CHMP also consulted the experts from the Infectious Disease Working Party (IDWP) regarding the dosing in multiple recurrences of CDI in the posology section of the SmPC; the IDWP supports the addition of recommendations in the Vancomycin SmPC in adults.

Based on the above, taking into account all available data and current knowledge regarding pharmacokinetics, the CHMP considers that the efficacy of vancomycin is established in the *"treatment of Clostridium difficile infection (CDI)"* (oral administration) in the revised posology.

Decontamination of the gastrointestinal tract in immune-compromised patients when combined with an aminoglycoside

The enteral administration of non-absorbable antimicrobials such as vancomycin, polymyxin E, tobramycin, and amphotericin B (PTA) should be viewed as one of the components of the selective decontamination of the gastrointestinal tract. The other three pillars of this strategy are a short course (4 days) of parenteral antibiotics, high levels of hygiene, and surveillance cultures of throat and rectum to monitor the effectiveness of the selective digestive decontamination and to detect resistance at an early stage.

The role of selective intestinal decontamination is still controversial. The concern of CHMP is whether this intervention could promote antibiotic resistance. Most of the data submitted in the procedure for this indication predate 2000. the most recent publications discussed, refers to the use of selective decontamination of the digestive tract and/or of the oropharyngeal tract for the prevention of lower tract infections and bloodstream infections in ICU patients or in patients with burns (Silvestri et al,

2004[14]; Cerda et al, 2007[15]). Similarly, a recent meta-review is discussed (Daneman et al., 2013) that showed no relationship between the use of selective decontamination and the development of antimicrobial resistance in pathogens in intensive care units. However, there is no consensus around the matter (Hurley et al., 2013[16]).

The CHMP questioned the evidence submitted by the MAH which mostly included data on the use of selective decontamination of the digestive tract for the prevention of lower tract infections and bloodstream infections in ICU patients and its extrapolation to immunocompromised patients; additional concerns from the CHMP were whether results seen in terms of prevention of lower respiratory tract infections and/or mortality can be applicable to any ICU regardless of the level of resistance. Furthermore, the claimed indication referred to immunocompromised patients and it remains unclear whether the results discussed for ICU patients were relevant to these patients who were assumed to be at high risk of systemic infection after allogeneic transplantation.

Having considered the uncertainties related to the potential benefit of using vancomycin in the decontamination of and taking the potential risks into account, the CHMP has concluded that the benefit/risk balance for vancomycin containing products in the indication *"Decontamination of the gastrointestinal tract in immune-compromised patients when combined with an aminoglycoside"* is negative.

Staphylococcal enterocolitis

Staphylococcal enterocolitis (SEC) has been recognized as a cause of antibiotic-associated diarrhoea since 1948, with a majority of the cases reported in medical literature originating from Japan. Common among the cases reported in the literature was the presence of a large volume of green diarrhoea which very likely is due to *S. aureus* primarily affecting the small intestine, while *C. difficile* is typically isolated to the colon or terminal ileum. Risk factors for the development of SEC in adults include age over 70 years, hospitalization, recent abdominal surgery, immunosuppression, human immunodeficiency virus, use of histamine-2 receptor antagonists, proton pump inhibitor therapy, colonization with *MRSA*, and prior use of antimicrobials (particularly fluroquinolones). *SEC* should be suspected in patients who have recently completed a course of fluoroquinolones or beta-lactam antibiotics and have an enteric culture positive for *S. aureus* with an absence of normal gram-negative flora (Avry LM et al, 2015). *C. difficile* testing should be negative. Overall, *SEC* seems to be a rare entity and further information was requested by the CHMP to the MAHs to justify the benefit risk balance of this indication, including an updated review of scientific literature, therapeutic guidelines.

The elements submitted by the MAHs did not establish adequately the efficacy and safety in this indication. Most of the MAHs agreed that *staphylococcal enterocolitis* is a very rare condition. Some MAHs described sporadic case reports from literature, where vancomycin treatment has been successful. However, updated clinical guidelines for *staphylococcal enterocolitis* diagnosis or treatment do not mention this use. Whilst there are reports suggesting that *S. aureus* could cause rarely enterocolitis, the validity of *S. aureus* as a cause of enterocolitis is controversial albeit rarely.In view of the lack of robust data establishing the efficacy and safety in this indication.

The CHMP therefore considers that the benefit risk balance is negative and the indication should be removed from the SmPC.

Conclusion:

14 Silvestri, L., et al. "Prevention of MRSA pneumonia by oral vancomycin decontamination: a randomised trial." *European Respiratory Journal* 23.6 (2004): 921-926
15 Cerdá, Enrique, et al. "Enteral vancomycin controls methicillin-resistant Staphylococcus aureus endemicity in an intensive care burn unit: a 9-year prospective study." *Annals of surgery* 245.3 (2007): 397-407
16 Hurley, J. C. (2013). Studies of selective decontamination. *The Lancet Infectious Diseases*, *13*(9), 736

Based on the above assessment, the CHMP concluded that consideration should be given to official guidance on the appropriate use of antibacterial agents and the benefit risk of the following indications for vancomycin-containing products is favourable:

- *For powder for concentrate for solution for infusion*

[For vancomycin powder for concentrate for solution for infusion authorised for parenteral administration, the indication should be as follows:]

Intravenous administration

Vancomycin is indicated in all age groups for the treatment of the following infections (see sections 4.2, 4.4 and 5.1):

- complicated skin and soft tissue infections (cSSTI)

- bone and joint infections

- community acquired pneumonia (CAP)

- hospital acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP)

- infective endocarditis

[For parenteral formulations authorised for the following indications:]

- acute bacterial meningitis

- bacteraemia that occurs in association with, or is suspected to be associated with, any of the above.

- Vancomycin is also indicated in all age groups for the perioperative antibacterial prophylaxis in patients that are at high risk of developing bacterial endocarditis when undergoing major surgical procedures.

[For parenteral formulations authorised for intraperitoneal use, the indication should be as follows:]

Intraperitoneal administration

Vancomycin is indicated in all age groups for the treatment of peritoneal dialysis–associated peritonitis (see sections 4.2, 4.4 and 5.1).

[For vancomycin powder for concentrate authorised for oral administration, the following should be reflected in this section]

[For parenteral formulations authorised for oral use, the indication should be as follows:]

Oral administration

Vancomycin is indicated in all age groups for the treatment of *Clostridium difficile* infection (CDI) (see sections 4.2, 4.4 and 5.1).

[The below wording should be introduced in this section for all vancomycin containing products]

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

- For Oral Capsules

Vancomycin capsules are indicated in patients 12 years and older for the treatment of Clostridium difficile infection (CDI) (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

2.3.1.3. Posology and method of administration in subpopulations

The CHMP also reviewed the dosage regimen for vancomycin for the various approved indications and patient subpopulations.

The CHMP noted that a general recommendation stating that the dose should be individually adapted according to weight, age and the underlying type and severity of infection and clinical response is not included in all SmPCs. In order to achieve the optimal trough concentration, the CHMP is of the opinion that the doses should be calculated based on the body weight and that a general statement should be included in the section 4.2 accordingly.

Adult population

Specific questions with regards to the dosing regimen, use of surrogate markers for exposure, therapeutic drug monitoring (TDM) and continuous infusion were asked by the CHMP to IDWP, Pharmacokinetics Working Party (PKWP) and Modelling and Simulation Working Group (MSWG). The recommendations were as follows:

1. Regarding the value of the general recommendation "usual dose" (2 g/day) instead of weight-based regimen, considering that this dose may be not appropriate in a substantial proportion of cases, the IDWP agrees that the 2 g/day dose often results in trough values below the target of 10 to 20 mg/L and therefore the IDWP agrees that the usual dose should be deleted and recommends the use of a weight based dosage regimen (15-20 mg/kg body weight every 8-12 hours). The CHMP agrees with IDWP conclusions.

2. In addition, regarding the recommendation concerning the use of Bayesian methods to guide the dose, the IDWP and MSWG concludes that Bayesian methods are clinically useful for more accurate dose predictions as a complementary part of routine TDM monitoring and acknowledges that this is already used in clinical use. The CHMP noted that, while the use of Bayesian methods to guide the dose in individual patients could be used in those cases in which trough levels would not be predictive (e.g. use of very high doses of 4 g/day), it would be difficult to include any useful recommendation to the practitioner in the SmPC. However the CHMP considered that the optimisation schemes based on nomograms and Bayesian interpolation seem to be the most appropriate; they allow predicting many individual pharmacokinetic parameters for extrapolation, minimize the number of measurements on a single patient and seem to develop optimal strategies for therapeutic intervention. In addition, in line with the outcome of the MSWG consultation, the CHMP concluded that Bayesian methods are 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 ("Model-based methods may be useful in the prediction of individual dose requirements to reach an adequate AUC. The model-based approach can be used both in calculating the personalized starting dose and for dose adjustments based on TDM results.")*.*

3. The CHMP acknowledged that many reports published in the medical literature indicate that administration of vancomycin as continuous infusion may reduce the known toxicity of vancomycin. Nevertheless, comparative data obtained using continuous versus intermittent administration rendered conflicting results. Moreover, currently available data do not point towards improved outcomes in patients in which vancomycin was administered via continuous infusion versus those that received intermittent treatment. Because of the above, no firm recommendation on the use of a continuous infusion could be made. IDWP also discussed this

topic and agreed that, despite the continuous administration was used in clinical practice, the currently available evidence was not supportive of including a statement on continuous administration in the Vancomycin SmPC for IV use.

4. Finally, the CHMP also consulted the IDWP and MSWG regarding the recommendations for therapeutic drug monitoring (particularly, the frequency of TDM in haemodynamically stable and unstable patients). The IDWP discussed the existing TDM target recommendations and agreed that the existing evidence does not allow at present any revision of the existing SmPC wording. 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, 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; the CHMP also 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 agrees with the above mentioned conclusions.

Paediatric population

The CHMP also reviewed the dose recommendation for the paediatric population. Across the different SmPC in the European Union, the same dose recommendation is given across the SmPCs for children (from 1 month up to 12 years old):

- Children (1 month to 12 years): The intravenous daily dose should be 40 mg/kg body weight, mostly in 4 single doses, that is 10 mg/kg body weight every 6 hours. The dose may be increased to 60 mg/kg bodyweight per day;

- Infants up to 1 month: For young infants and newborns the doses can be lower. The recommendation is an initial dose of 15 mg/kg body weight and maintenance doses of 10 mg/kg body weight every 12 hours in the first life week and then every 8 hours until the age of one month. The blood concentrations of vancomycin should be monitored.

Questions with regards to dosing regimen in children, specifically on the recommended maximum daily dose (60 mg/kg/day) were asked by the CHMP to PDCO. The recommendations were as follows:

1. 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 approved vancomycin-containing medicines already include some dosing recommendations for both term and preterm neonates[17]. 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 for neonates, the advice of a physician experienced in the management of neonates should be sought. The SmPC has been amended accordingly by the CHMP, including the dosing regimen in children based on post-menstrual age as a possible way of dosing vancomycin in this population.

17 http://www.medicines.org.uk/emc/medicine/20836)

2. Regarding the administration of vancomycin as a continuous infusion in paediatric patients, the 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 bacteraemia. 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. As a consequence, no dosing recommendations for continuous infusion could be issued in the SmPC.

3. The CHMP also noticed that there is no agreement on the recommended maximum daily dose (60 mg/kg/day) in children. The CHMP consulted the PDCO to obtain information on clinical practice. Regarding the dosing in children, the PDCO discussed whether doses higher than 60 mg/kg/day may be needed in selected paediatric patients as in them even this dose may not achieve the target vancomycin trough level. The PDCO is of the view that current dosing recommendations of 15 mg/kg every 6 hours in children from 6 months to less than 12 years older may result in a substantial number of paediatric patients not reaching the vancomycin trough level recommended in case of serious infections. However, there is insufficient evidence to recommend the use of doses higher than 15 mg/kg every 6 hours and therefore no proposal is made by the PDCO in this respect in the absence of clear recommendations for monitoring vancomycin levels based on AUC/MIC ratio. The CHMP agrees with PDCO conclusions.

4. The CHMP also reviewed the dose adjustment in children: based on PDCO recommendation, the CHMP is of the opinion that dose adjustments in paediatric patients aged 1 year and older based on glomerular filtration rate estimated (eGFR), including a guidance-table in the section 4.2 of the SmPC are warranted. The CHMP also recommends monitoring of vancomycin levels to adjust the dose.

Other special populations

The CHMP also reviewed the recommendations for specific populations (elderly, renal impairment population, pregnancy and obese patients) and amended the wording accordingly for intravenous administration:

- For elderly populations, lower maintenance doses may be required due to the age-related reduction in renal function.
- For adult and paediatric patients with renal impairment, consideration should be given to an initial starting dose followed by serum vancomycin trough levels rather than to a scheduled dosing regimen. In patients with mild or moderate renal impairment, the starting dose must not be reduced. Appropriate consideration should be given to the concomitant administration of medicinal products that may reduce vancomycin clearance and/or potentiate its undesirable effects.
- Significantly increased doses may be required to achieve therapeutic serum concentrations in pregnant women.

- The dosing in obese patients shouldl be based on body weight and the initial dose should be individually adapted according to total body weight as in non-obese patients.
- No dose adjustment is needed in patients with hepatic insufficiency.

Other amendments proposed

Amendments of this section for including information related to intraperitoneal and oral administrations, monitoring of vancomycin serum concentrations and method of administration were also performed for adults and paediatric populations accordingly, as relevant.

2.3.2. Safety

The CHMP also reviewed the data on adverse events observed with the use of vancomycin.

With regards to the ***Undesirable effects*** the CHMP noticed that most of the below common adverse reactions are mentioned in the SmPCs of vancomycin-containing products:

- severe acute hypersensitivity reactions,
- neutropenia in long term use / concomitant use with other drugs which may cause neutropenia or agranulocytosis,
- ototoxicity,
- infusion related reactions, “red man’s syndrome”,
- infusion related reactions in co-administration with anaesthetics,
- myocardial depression in co-administration with anaesthetics,
- extravasation, necrosis,
- thrombophlebitis,
- chemical peritonitis in intraperitoneal use,
- teicoplanin cross-reactivity reactions,
- nephrotoxicity,
- pseudomembranous colitis.

The data included in the SmPCs appear in line with the published safety information (e.g. Bruniera 2015). Also the measures discussed in the literature to reduce unwanted effects are those included or proposed to be included in the SmPC: individualised dosing, renal function monitoring, TDM, appropriate duration of use, consideration of concomitant medication, avoidance of use in pre-existing hearing loss.

A literature search was undertaken in MEDLINE in order to assess data on safety of vancomycin (cut-off date 16 June 2016). The safety issues discussed most in the literature are nephrotoxicity and ototoxicity, but also infusion related problems like vein and tissue toxicity as well as hypersensitivity reactions. A brief summary of relevant articles is described below.

Nephrotoxicity is one of the most important safety concerns relating to vancomycin. Although the exact mechanism of vancomycin-induced renal toxicity is not well defined, the most probable mechanism for this nephrotoxicity is an increase in the production of reactive oxygen species and oxidative stress.

Some studies have reported that there are some susceptibility factors which could accelerate or potentiate the occurrence of vancomycin nephrotoxicity. The most highly documented risk factors are:

- high trough vancomycin level (especially >20 mg/L) or doses (>4g/day),
- treatment with concomitant nephrotoxicity agents,
- prolonged therapy (even more than 7 days),
- prolonged stay in an intensive care unit.

In another Phase I study, statistical analysis identified vancomycin serum trough concentrations ≥ 14mg/L, duration of vancomycin therapy ≥ 7 days, and baseline serum creatinine levels ≥ 1.7mg/dL as independent predictors of nephrotoxicity.

Another frequently quoted adverse event is ototoxicity, caused by direct damage in auditory nerve.

Most patients presented renal dysfunction or pre-existing hearing loss. Forouzesh et al[18] in their retrospective case-control study conclude that a significant rate of high-frequency hearing loss in older patients receiving vancomycin monotherapy is detected by audiometry.

Other adverse events reported also seem to largely correspond with what is already included in the SmPC. They include hypersensitivity reactions, macular cutaneous rash and anaphylaxis, urticaria, hypotension, dyspnoea or itching; events related to infusion, pain, phlebitis, erythema, urticaria, flushing, hypotension, tachycardia and red man syndrome.

The CHMP acknowledged that the use of vancomycin for parenteral use is associated with nephrotoxicity and ototoxicity, as well as infusion related adverse reactions like vein and tissue toxicity as well as hypersensitivity reactions. Vancomycin is known to cause renal impairment, and renal function monitoring is critical in patients with renal impairment (including elderly patients). The CHMP agreed these risks must be mitigated by warnings and recommendations in the SmPC to ensure regular renal function testing. Regular vancomycin therapeutic drug monitoring is indicated in prolonged treatment, especially in patients with previous renal impairment, or hearing loss, and concomitant nephro-(and oto-) toxic drugs.

Vancomycin should be used with caution in premature newborns and in infants, because of their renal immaturity and possible increase in serum concentrations of the drug. Therefore, vancomycin blood levels should be monitored carefully.

The use of vancomycin in patients with a previous diagnostic of hearing loss is not recommended.

The product information is amended to reflect the above recommendations.

2.3.3. Pharmacological properties

2.3.3.1. Mechanism of action

Vancomycin is a tricyclic glycopeptide antibiotic that inhibits the synthesis of the cell wall in sensitive bacteria by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall precursor units.

18 Forouzesh, Avisheh, Pamela A. Moise, and George Sakoulas. "Vancomycin ototoxicity: a reevaluation in an era of increasing doses." *Antimicrobial agents and chemotherapy* 53.2 (2009): 483-486

The effect of Vancomycin is mainly bactericidal and is exerted mainly by the inhibition of the cell wall peptidoglycan synthesis.

2.3.3.2. Mechanism of resistance and EUCAST breakpoints

Mechanism of resistance

Acquired resistance to glycopeptides is most common in enterococci and is based on acquisition of various van gene complexes which modifies the D-alanyl-D-alanine target to D-alanyl-D-lactate or D-alanyl-D-serine which bind vancomycin poorly. In some countries, increasing cases of resistance are observed particularly in *enterococci*; multi-resistant strains of *Enterococcus faecium* are especially alarming.

Van genes have rarely been found in *Staphylococcus aureus*, where changes in cell wall structure result in "intermediate" susceptibility, which is most commonly heterogeneous. Also, *methicillin-resistant staphylococcus* strains (MRSA) with reduced susceptibility for vancomycin were reported. The reduced susceptibility or resistance to vancomycin in *Staphylococcus* is not well understood. Several genetic elements and multiple mutations are required.

There is no cross-resistance between vancomycin and other classes of antibiotics. Cross-resistance with other glycopeptide antibiotics, such as teicoplanin, has been reported. Secondary development of resistance during therapy is rare.

Susceptibility testing breakpoints

The CHMP noted the recent evidence on poorer clinical outcomes in patients infected with *S. aureus* with a vancomycin MIC above 1 mg/L. Discussions with EUCAST confirmed however that changes to the currently recommended EUCAST breakpoints for *staphylococci* were not warranted.

It was decided to add a warning in section 4.4 under Spectrum of antibacterial activity subheading, to clarify that vancomycin is active mainly against gram-positive aerobic and anaerobic bacteria. *Clostridium difficile* is sensitive to orally administered vancomycin. Vancomycin is not active against Gram-negative bacilli, mycobacteria or fungi.

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. This information only provides approximate guidance on the chance whether micro-organisms are susceptible to vancomycin.

Minimum inhibitory concentration breakpoints established by the EUCAST are as follows:

Table 1 Minimum inhibitory concentration breakpoints established by the EUCAST

	Susceptible	Resistant
Staphylococcus spp. [1]	≤ 2 mg/L	> 2 mg/L
Enterococcus spp[1].	≤ 4 mg/L	> 4 mg/L
*Gram positive anaerobes (*except *Clostridium difficile)*	≤ 2 mg/L	> 2 mg/L
Clostridium difficile[2]	≤ 2 mg/L	> 2 mg/L

1Non-susceptible isolates are rare or not yet reported. The identification and antimicrobial susceptibility test result on any such isolate must be confirmed and the isolate sent to a reference laboratory.

2 The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.

2.4. Consultation of QWP, IDWP, PDCO, PKWP and MSWG as well as external experts (EUCAST)

Consultations with the Paediatric Committee (PDCO) and CHMP working parties/groups (Infectious Disease (IDWP), Pharmacokinetics (PKWP) and Quality (QWP) Working Parties, and Modelling and Simulation Working Group (MSWG)) took place in the context of the procedure. External experts (the European Committee on Antimicrobial Susceptibility Testing, EUCAST) were also consulted by the CHMP.

The CHMP consulted the IDWP to CHMP sought the view of IDWP on a number of aspects. Regarding the acceptability of the available PK/PD data as supportive of the dose recommendations proposed by the CHMP, the IDWP recognised the limitations of the PK/PD data but agreed that they could be taken into account to determine dosage recommendations, including for loading and maintenance doses and in the relevant patient populations. The advice of the IDWP was taken into account by the CHMP when revising the SmPC wording. For instance, some guidelines recommend continuous infusion in specific situations, such as obese patients, children or for specific indications such as peritonitis. Finally, some specific issues were also addressed such as the general recommendation “usual dose” (2 g/day) instead of weight-based regimen is questioned, the value of continuous infusion in specific patients, the dosing in children, the frequency of TDM in haemodynamically stable and unstable patients and the prophylaxis against bacterial endocarditis, the use of Bayesian methods to guide the dose and the dosing in recurrences of CDI. The use of Bayesian methods to guide the dose was also addressed by the MSWG and the PKWP.

Specific questions with regards to the dosing regimen in children, specifically on the recommended maximum daily dose (60 mg/kg/day) were also addressed by the PDCO, at the request of CHMP.

Finally, the CHMP also consulted the QWP regarding specification for related substances in both the active substance and the finished products. It was clarified that that the scope of the CHMP guideline on setting specifications for related impurities in antibiotics applies to new active substances and for new sources of existing active substances. Hence, the identification and qualification thresholds proposed in the guideline (0.15%) should be applied to new substances or finished products for which impurities are not qualified. Finally, it was notes that the Ph. Eur. monograph for vancomycin is under revision. Once the revised Ph. Eur. monograph enters into force, the limits of the impurities in the active substance and finished products will need to be revised/updated accordingly, where applicable.

2.5. Risk management

The CHMP, having considered the available data, is of the opinion that neither additional pharmacovigilance activity, nor additional risk minimisation measure are required beyond the recommended changes to the product information.

2.5.1. Changes to the product information

Having reviewed all available data, the CHMP considered that a number of changes are needed to the product information of vancomycin-containing products for the powder for concentrate for solution for

infusion and capsule formulations. In particular, the wording of the indications was revised and aligned with the available data and taking into consideration the existing clinical experience and current guidelines. Because the available data do not adequately support the use of vancomycin in the treatment of staphylococcal enterocolitis (inflammation of the gut caused by *S. aureus*) and its use to clear the gut of bacteria in patients with a weakened immune (defence) system, the CHMP concluded that vancomycin should no longer be used for these indications.

The posology and method of administration section was also significantly revised to provide appropriate and up-to-date guidance on the use of vancomycin to prescribers. The available data confirms that vancomycin exhibits nephrotoxicity and ototoxicity, infusion related adverse reactions as well as hypersensitivity reactions. These risks can however be mitigated by appropriate statements in section 4.4 including warnings against potential for systemic absorption, nephrotoxicity, ototoxicity, drug interactions, development of drug-resistant bacteria and recommendations for regular renal function monitoring.

Information on warnings and precautions for use were overall consistent across the SmPCs of vancomycin-containing products, with overlaps in some cases. Additional changes were agreed to the section 4.4, to streamline information in this section, moving across information pertaining to the dosing, monitoring and appropriate use into relevant sections accordingly. 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 also agreed corresponding changes to the package leaflets.

2.6. Benefit-risk balance

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[19,20]) and Infectious Diseases Society of America (IDSA[21]) 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[22], IDSA[23]

19 ESCMID guidelines: https://www.escmid.org/escmid_publications/medical_guidelines/escmid_guidelines/
20 ESCMID guideline
https://www.escmid.org/fileadmin/src/media/PDFs/4ESCMID_Library/2Medical_Guidelines/ESCMID_Guidelines/Eu_Rec_Antimicrobal.pdf
21 IDSA guideline
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Antimicrobial_Agent_Use/Vancomycin/Vancomycin/
22 Bacterial meningitis:ESCMID guideline for bacterial meningitis: http://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(16)00020-3/abstract
23 IDSA:
http://www.idsociety.org/Guidelines/Patient_Care/IDSA_Practice_Guidelines/Infections_by_Organ_System/Central_Nervous_System_(CNS)/Bacterial_Meningitis/

guideline and UK joint specialist societies guidelines[24], 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[25]), the ISPD recommendations for pediatric patients (Warady BA et al., 2012[26]). 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[27,28] 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.

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.

24 Joint guideline: https://www.britishinfection.org/files/5614/5674/2938/McGill_meningitis_guidelines_Final_published_proof.pdf
25 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
26 ISPD recommendations for paediatric patients (Warady BA et al., 2012) - https://ispd.org/media/pdf/Consensus__Change_20_.pdf
27https://www.escmid.org/fileadmin/src/media/PDFs/4ESCMID_Library/2Medical_Guidelines/ESCMID_Guidelines/fulltext_treatment_guidance_Clostridium_difficile_infection.pdf
28 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 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[29]. 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.

29 http://www.medicines.org.uk/emc/medicine/20836

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.

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.

3. Conclusion and grounds for opinion

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.

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