NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC

E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 31 of Directive 2001/83/EC to the CHMP made by Spain

Active Substance	vancomycin containing products

Vancomycin is a glycopeptide antibiotic developed 60 years ago. It exerts its slow bactericidal effect 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.* The use of vancomycin was questioned in the middle of the last century due to ototoxic and nephrotoxic adverse effects related to impurities in the formulation, but more recent formulations came up to solve this problems, and toxicity has been considerably reduced because of that quality improvement although caution is still needed when vancomycin is co-administer with other nephrotoxics like aminoglycosides, or when renal impairment is established or when used at high doses.

Vancomycin-containing products are commercially available as vancomycin (hydrochloride) 500 mg, 1000 mg powder for solution for injection. Vancomycin is also administered by the oral route for the treatment of *Clostridium difficile*-associated diarrhoea (CDAD).

Vancomycin hydrochloride is defined as the hydrochloride of a mixture of related glycopeptides and is subject to the European Pharmacopeia 1058 monograph which is currently under revision. In accordance with the monograph in force the substance is obtained by fermentation or by other means.

From a quality point of view, the CHMP should also consider whether the limits for components and impurities in the drug substance (and in drug products if appropriate) are adequate.

In addition, discussions should take place on how to best express the strengths of vancomycin products in view of the current global clinical practices.

The antibacterial activity of vancomycin is confined to Gram-positive microorganisms. From a clinical point of view, 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 *S. aureus* (MRSA), coagulase-negative staphylococci (CoNS) and enterococci, the latter often tolerant to β-lactam antibiotics. It is also indicated for patients who are allergic to penicillins and cephalosporins. Oral vancomycin is also used for the treatment of *Clostridium difficile*-associated diarrhoea (CDAD).

However, increases in the rates of heteroresistance and tolerance to vancomycin, combined with its pharmacodynamic (slow bactericidal activity, variable tissue penetration etc.) and clinical (clinical failures reported in patients with invasive infections and a MIC above 1 mcg/mL against *S. aureus*) shortcomings as well as the increasingly important role of Gram-positive bacterial infections in the clinical setting, have triggered a debate on 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 and safe antibiotics for the EU patients, in the interest of public health and in order to contribute to an efficient response to the threat posed by the spread of antimicrobial resistance, it is considered that there is a need for a critical review of the benefit-risk of vancomycin-containing products in the approved indications, including the relevant posology.

In addition, as is the case with many antibacterials which have been put on the market decades ago, there are significant differences between the product information of vancomycin-containing medicines across the EU Member States, importantly in the approved indications, posology, but also in other important sections of the Product Information. As a consequence of the divergences above and the need to update the Product Information in light of the available information, there is a need to review the benefit-risk for vancomycin-containing medicinal products approved in the EU Member States and to update accordingly the Product Information, in particular sections 4.1-4.4 (e.g. update of the dosing recommendations taking into consideration the infection site and pathogen susceptibility, dosing recommendations for preterm children given the use of vancomycin in neonatal intensive care units, dosing recommendations for the CDAD including for paediatric patients the update of the optimal trough vancomycin concentrations for intravenous administration,...), 4.8, 5.1 and 5.2 of the Summary of Product Characteristics.

In view of the above and the necessity to take action at the EU level, Spain considers that it is in the interest of the Union to refer the matter to the CHMP and requests that it 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

Signed [redacted]

Date 21st March 2016