

## SUMMARY OF PRODUCT CHARACTERISTICS

### 1 NAME OF THE MEDICINAL PRODUCT

Vancomycin 125 mg hard capsules

### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 125 mg vancomycin hydrochloride equivalent to 125,000IU vancomycin.

For the full list of excipients, see section 6.1.

### 3 PHARMACEUTICAL FORM

Capsule, hard

Grey/pink  $17.8 \pm 0.40$  mm hard capsule, containing white to off white congealed liquid mixture as solid mass.

### 4 CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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.

#### 4.2 Posology and method of administration

##### Posology

*Adults and adolescents aged 12 to less than 18 years old*

The recommended vancomycin dose is 125 mg every 6 hours for 10 days for the first episode of non-severe CDI. This dose can be increased to 500 mg every 6 hours for 10 days in case of severe or complicated disease. The maximum daily dose should not exceed 2 g.

In patients with multiple recurrences, consideration may be given to treat the current episode of CDI with vancomycin, 125 mg four times daily for 10 days followed by either tapering the dose, i.e., gradually decreasing it until 125 mg per day or a pulse regimen, i.e., 125–500 mg/day every 2–3 days for at least 3 weeks.

Treatment duration with vancomycin may need to be tailored to the clinical course of individual patients. Whenever possible the antibacterial suspected to have caused CDI should be discontinued. Adequate replacement of fluid and electrolytes should be instituted.

Monitoring vancomycin serum concentrations after oral administration in patients with inflammatory intestinal disorders should be performed (see section 4.4).

## Special populations

### *Renal impairment*

Due to the very low systemic absorption, dose adjustment is unlikely, unless substantial oral absorption may occur in case of inflammatory intestinal disorders or *Clostridium difficile*-induced pseudomembranous colitis (see section 4.4).

### *Paediatric population*

Vancomycin capsules are not appropriate for the treatment of children under the age of 12 years or for adolescents unable to swallow them. Below 12 years, age-appropriate formulation should be used.

## Method of administration

For oral use.

The capsule should not be open and should be taken with plenty of water.

## **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients (see section 6.1).

## **4.4 Special warnings and precautions for use**

### **Oral Use Only**

This preparation is for oral use only and is not systemically absorbed. Orally administered Vancomycin capsules are not effective for other types of infections.

### **Potential for Systemic Absorption**

Absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or *Clostridium difficile*-induced pseudomembranous colitis. These patients may be at risk for the development of adverse reactions, especially if there is a concomitant renal impairment. The greater the renal impairment, the greater the risk of developing the adverse reactions associated with the parenteral administration of vancomycin. Monitoring of serum vancomycin concentrations of patients with inflammatory disorders of the intestinal mucosa should be performed.

### **Nephrotoxicity**

Serial monitoring of renal function should be performed when treating patients with underlying renal dysfunction or patients receiving concomitant therapy with an aminoglycoside or other nephrotoxic drugs.

### **Ototoxicity**

Serial tests of auditory function may be helpful in order to minimise the risk of ototoxicity in patients with an underlying hearing loss, or who are receiving concomitant therapy with an ototoxic agent such as an aminoglycoside.

## **Drug interactions with anti-motility agents and proton pump inhibitors**

Anti-motility agents should be avoided and proton pump inhibitor use should be reconsidered.

## **Development of Drug-Resistant Bacteria**

Prolonged use of vancomycin may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

#### **4.5 Interaction with other medicinal products and other forms of interaction**

Concurrent and/or sequential systemic or topical use of other potentially ototoxic and/or nephrotoxic drugs requires careful monitoring.

#### **4.6 Fertility, pregnancy and lactation**

##### Pregnancy

Teratology studies have been performed at 5 times the human dose in rats and 3 times the human dose in rabbits, and have revealed no evidence of harm to the foetus due to vancomycin.

In a controlled clinical study, the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the drug was administered to pregnant women for serious staphylococcal infections complicating intravenous drug abuse. Vancomycin hydrochloride was found in cord blood.

No sensorineural hearing loss or nephrotoxicity attributable to vancomycin was noted. Vancomycin was administered only in the second and third trimesters; hence it is not known whether it causes foetal harm.

Consequently, vancomycin should only be given in pregnancy if clearly needed and after a careful benefit-risk assessment.

##### Breast-feeding

Vancomycin is secreted in breast milk and should therefore only be used during breast-feeding if other antibiotics have failed. In breast-fed infants, disorders of the intestinal flora with diarrhoea, fungus infection and possibly sensitisation may occur. It is recommended to stop breast-feeding during vancomycin treatment. Risks of systemic effects in premature and young neonates exposed to vancomycin in breast milk cannot be excluded due to relatively high intestinal permeability and immature elimination functions of these infants.

##### Fertility

Animal studies regarding effects on fertility are not available.

#### **4.7 Effects on ability to drive and use machines**

Vancomycin has no or negligible influence on the ability to drive and use machines.

#### **4.8 Undesirable effects**

##### Summary of the Safety profile

The absorption of vancomycin from the gastrointestinal tract is negligible. However, in severe inflammation of the intestinal mucosa, especially in combination with renal insufficiency, side effects that occur when vancomycin is administered parenterally may appear. Therefore, the below mentioned adverse reactions and frequencies related to parenteral vancomycin administration are included.

When vancomycin is administered parenterally, the most common adverse reactions are phlebitis, pseudo-allergic reactions and flushing of the upper body (“red-neck syndrome”) in connection with too rapid intravenous infusion of vancomycin.

Tabulated List of Adverse reactions

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The adverse reactions listed below are defined using the following MedDRA convention and system organ class database:

Very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ), not known (cannot be estimated from the available data).

<b>System organ class</b>	
<b>Frequency</b>	<b>Adverse reaction</b>
<b>Blood and lymphatic system disorders:</b>	
Rare	Reversible neutropenia <sup>1</sup> , agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia.
<b>Immune system disorders:</b>	
Rare	Hypersensitivity reactions, anaphylactic reactions <sup>2</sup>
<b>Ear and labyrinth disorders:</b>	
Uncommon	Transient or permanent loss of hearing <sup>4</sup>
Rare	Vertigo, dizziness, tinnitus <sup>3</sup>
<b>Cardiac disorders:</b>	
Very rare	Cardiac arrest
<b>Vascular disorders:</b>	
Common	Decrease in blood pressure
Rare	Vasculitis
<b>Respiratory, thoracic and mediastinal disorders:</b>	
Common	Dyspnoea, stridor
<b>Gastrointestinal disorders:</b>	
Rare	Nausea
Very rare	Pseudomembranous enterocolitis
Not known	Vomiting, Diarrhoea
<b>Skin and subcutaneous tissue disorders:</b>	
Common	Flushing of the upper body (“red man syndrome”), exanthema, and mucosal inflammation, pruritus, urticaria
Very rare	Exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, Linear IgA bullous dermatosis <sup>5</sup>
Not known	Eosinophilia and systemic symptoms (DRESS syndrome), AGEF (Acute Generalized Exanthematous Pustulosis)
<b>Renal and urinary disorders:</b>	

Common	Renal insufficiency manifested primarily by increased serum creatinine and serum urea
Rare	Interstitial nephritis Acute renal failure
Not known	Acute tubular necrosis
<b>General disorders and administration site conditions:</b>	
Common	Phlebitis, redness of the upper body and face.
Rare	Drug fever, shivering, Pain and muscle spasm of the chest and back muscles

#### Description of selected adverse drug reactions

<sup>1</sup> Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g.

<sup>2</sup> Intravenous vancomycin should be infused slowly. During or shortly after rapid infusion anaphylactic/anaphylactoid reactions including wheezing may occur. The reactions abate when administration is stopped, generally between 20 minutes and 2 hours. Necrosis may occur after intramuscular injection.

<sup>3</sup> Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment.

<sup>4</sup> Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicinal product like aminoglycoside, or in those who had a pre-existing reduction in kidney function or hearing.

<sup>5</sup> If a bullous disorder is suspected, the drug should be discontinued and specialized dermatological assessment should be carried out.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system, Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard) or search for MHRA Yellow Card in the Google Play or Apple App Store.

## **4.9 Overdose**

#### Treatment of overdose

Supportive care is advised, with maintenance of glomerular filtration. Vancomycin is poorly removed by dialysis. Haemofiltration and haemoperfusion with Amberlite resin XAD-4 have been reported to be of limited benefit.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1 Pharmacodynamic properties**

#### Pharmacotherapeutic group

Glycopeptide antibacterials, ATC code: A07AA09

### 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. The drug is bactericidal for dividing microorganisms. In addition, it impairs the permeability of the bacterial cell membrane and RNA synthesis. The drug is bactericidal for dividing microorganisms.

### 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 Dalanyl-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, does occur. Secondary development of resistance during therapy is rare.

### Susceptibility testing breakpoints

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. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable. This information only provides approximate guidance on the chance whether micro-organisms are susceptible to vancomycin.

Minimum inhibitory concentration breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are as follows:

	<b>Susceptible</b>	<b>Resistant</b>
<i>Clostridium difficile</i> <sup>1</sup>	≤ 2 mg/L	> 2 mg/L

<sup>1</sup> The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduced susceptibility.

## **5.2 Pharmacokinetic properties**

### Absorption

Vancomycin is not usually absorbed into the blood after oral administration. However, absorption may be enhanced in patients with inflammatory disorders of the intestinal mucosa or with *Clostridium difficile*-induced pseudomembranous colitis. This may lead to

vancomycin accumulation in patients with co-existing renal impairment.

### Elimination

An oral dose is excreted almost exclusively in the faeces. During multiple dosing of 250 mg every 8 hours for 7 doses, faecal concentrations of vancomycin, in volunteers, exceeded 100 mg/kg in the majority of samples. No blood concentrations were detected and urinary recovery did not exceed 0.76%.

## **5.3 Preclinical safety data**

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Limited data on mutagenic effects show negative results; long-term studies in animals regarding a carcinogenic potential are not available. In teratogenicity studies, where rats and rabbits received doses approximately corresponding to the human dose based on body surface ( $\text{mg}/\text{m}^2$ ), no direct or indirect teratogenic effects were observed.

Animal studies of the use during the perinatal/postnatal period and regarding effects on fertility are not available.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### Capsule content:

Polyethylene glycol (Macrogol) 6000

#### Capsule cap and body:

Gelatin

Colorants:

Iron oxide Yellow (E172)

Iron oxide Red (E172)

Titanium dioxide (E171)

Iron Oxide Black (E172)

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

24 months.

### **6.4 Special precautions for storage**

Do not store above 25° C.

### **6.5 Nature and contents of container**

AL-PVC/PE/Aclar blister packs of 4 capsules or 12 capsules or 20 capsules or 28 capsules or 30 capsules. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

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Trading as: Co-pharma

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03/12/2014

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