

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin 125mg Capsules, Hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 128.15mg of vancomycin hydrochloride equivalent to 125,000 IU vancomycin base.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Capsule(s), hard.

Opaque blue and opaque brown hard capsule(s)

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).

Vancomycin is not significantly absorbed from the normal gastro-intestinal tract and is therefore not effective by the oral route for other types of infection. Intravenous administration may be used concomitantly if required.

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

4.2 Posology and method of administration

Posology:

Adults, 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

Vancomycin Capsules is contraindicated in patients with known hypersensitivity to vancomycin or any of the excipients listed in 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.

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.

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.

Drug interactions with anti-motility agents and proton pump inhibitors

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

Severe cutaneous adverse reactions (SCARs)

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

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 If signs and symptoms suggestive of these reactions appear, vancomycin should be withdrawn immediately and an alternative treatment considered.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

Development of Drug-Resistant Bacteria

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

Cardiovascular and cerebrovascular effects

Cases of Kounis syndrome have been reported in patients treated with vancomycin. Kounis syndrome has been defined as cardiovascular symptoms secondary to an allergic or hypersensitive reaction associated with constriction of coronary arteries and potentially leading to myocardial infarction.

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.

Consideration should be given to discontinuing proton pump inhibitors and anti-motility agents in line with local guidelines for treatment of *Clostridium difficile* infection.

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. One infant, whose mother received vancomycin in the third trimester, experienced conductive hearing loss that was not attributable to vancomycin. Because vancomycin was administered only in the second and third trimesters, it is not known whether it causes foetal harm. Therefore vancomycin should be given to a pregnant woman only if clearly needed.

Breast-Feeding

Vancomycin hydrochloride is excreted in human milk. Caution should be exercised when vancomycin is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Not relevant.

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.

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

Tabulated List of Adverse reactions

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).

Blood and the lymphatic system disorder:

Rare: Reversible neutropenia, reversible agranulocytosis, eosinophilia, thrombocytopaenia, pancytopenia.

Not known: haemolytic anaemia

Immune system disorders:

Rare: Anaphylactic reactions, hypersensitivity reactions.

Ear and labyrinth disorders:

Rare: Tinnitus, dizziness, vertigo.

Uncommon: Transient or permanent loss of hearing.

Cardiac disorders

Very rare: Cardiac arrest

Not known: Kounis syndrome

Vascular disorders:

Common: Decrease in blood pressure.

Rare: Vasculitis.

Respiratory, thoracic and mediastinal disorders:

Common: Dyspnoea, stridor.

Gastrointestinal Disorders:

Rare: Nausea.

Very rare: Pseudomembranous enterocolitis.

Not known: Vomiting, diarrhoea

Skin and subcutaneous tissue disorders:

Common: Flushing of the upper body (“red man syndrome”), exanthema and mucosal inflammation, pruritus, urticaria.

Very rare: Exfoliative dermatitis, Stevens-Johnson syndrome, Toxic epidermal necrolysis (TEN), Linear IgA bullous dermatitis.

Not known: Eosinophilia and systemic symptoms (DRESS syndrome), AGEP (Acute Generalized Exanthematous Pustulosis).

Renal and urinary disorders:

Common: Renal insufficiency manifested primarily by increased serum creatinine or serum urea concentrations.

Rare: Interstitial nephritis, acute renal failure.

Not known: Acute tubular necrosis

Hepatobiliary disorders:

Common: alanine aminotransferase increased, aspartate aminotransferase increased

General disorders and administration site conditions:

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

Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g.

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.

Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment.

Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicinal products, or in those who had a pre-existing reduction in kidney function or hearing.

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 Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 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: Antibiotics, ATC Code: A07 AA09.

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.

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 antibiotics but 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:

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

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

5.2 Pharmacokinetic properties

Absorption

Orally administered vancomycin does not usually enter the systemic circulation even when inflammatory lesions are present. Measurable serum concentrations may infrequently occur in patients with active *C.difficile*-induced pseudomembranous colitis, and, in the presence of renal impairment, the possibility of accumulation exists. Vancomycin is poorly absorbed from the gastro-intestinal tract.

Elimination

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

Administration of vancomycin oral solution, 2 g daily for 16 days, to anephric patients with no inflammatory bowel disease, gave serum levels of <0.66 µg/ml. With doses of 2 g daily, concentrations of >3, 100 mg/kg can be found in the feces, and levels of <1 µg/ml can be found in the serum of patients with normal renal function who have pseudomembranous colitis.

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 (mg/m²), 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

Each hard capsule contains the following excipient: polyethylene glycol

Capsule shell components

Gelatin

FD & C blue no.2 lake (E132)

Iron oxide red (E172)

Iron oxide yellow (E172)

Purified water

Sodium lauryl sulphate

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

18 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Keep blisters in the outer carton to protect from moisture.

6.5 Nature and contents of container

Clear transparent PVC/ACLAR* film and Aluminium lidding foil.

Blister packs of 10, 14, 15, 20, 28, 30, 56, 60, 84, 90 and 112 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

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

7 MARKETING AUTHORISATION HOLDER

Morningside Healthcare Limited,
115 Narborough Road, Leicester,
LE3 0PA
UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 20117/0149

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16/01/2014

10 DATE OF REVISION OF THE TEXT

08/01/2026