SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Vancomycin Capsules 250mg

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3 PHARMACEUTICAL FORM

Capsules

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 to500 mg i 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 capsules 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 4.4).

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 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 treatment with an ototoxic drug such as an aminoglycoside.

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.

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

Since there is a risk for systemic absorption (see section 4.4), concomitant and/or subsequent systemic or topical use of other potentially ototoxic and/or nephrotoxic medicinal products should be monitored with great care.

Parenteral administration of vancomycin and anesthetics may cause erythema and anaphylactic reactions.
Some antibiotics were rarely reported to reduce the effect of oral contraceptives by interfering with the bacterial hydrolysis of conjugated steroids in the intestine and thus reabsorption of unconjugated steroid. This would lower the plasma levels of active steroid. This unusual interaction would occur in women with high excretion of conjugated steroids in bile.

4.6 Fertility, pregnancy and lactation

Pregnancy: There is insufficient experience on the use of Vancomycin during pregnancy. The safe use of vancomycin during pregnancy has not been established.

Reproductive studies in animals at doses equivalent to the clinical dose based on body surface area (mg/m^3), do not indicate any direct or indirect effects on embryonic development, foetus or gestation.

Vancomycin should only be administered to pregnant women after a careful benefit-risk assessment.

Breastfeeding: Vancomycin is secreted in breast milk and should therefore only be used during lactation if other antibiotics have failed. It is recommended to stop breast-feeding during vancomycin treatment.

Fertility: No definitive fertility studies have been conducted.

4.7 Effects on ability to drive and use machines

Vertigo and dizziness have been reported rarely, and may affect 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.

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

System organ class	
Frequency	**Adverse reaction**
Blood and the lymphatic system disorders:	
Rare	Reversible neutropenia[1], agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia.
Immune system disorders:	
Rare	Hypersensitivity reactions, anaphylactic reactions[2]
Ear and labyrinth disorders:	
Uncommon	Transient or permanent loss of hearing[4]
Rare	Vertigo, tinnitus[3], dizziness
Cardiac disorders:	
Very rare	Cardiac arrest
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 dermatosis[5]
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 and serum urea
Rare	Interstitial nephritis, acute renal failure
Not known	Acute tubular necrosis
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.

Otoxicity has primarily been reported in patients given high doses, or in those with concomitant treatment with other ototoxic medicinal product like aminoglycoside, 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 at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Toxicity: Limited experience in overdose, however, 500mg IV given to a 2-year-old lead to lethal intoxication. 56g spread over 10 days to an adult caused renal insufficiency.

Symptoms: Overdose may cause nausea, vomiting, epigastric discomfort and diarrhea. Possible symptoms that have been reported as side effects (see section 4.8) are exacerbated at overdose.

Effects on renal function may occur.

Treatment: Gastric lavage, charcoal in repeated doses (reducing half-life). Ensure adequate diuresis.

Vancomycin is poorly removed from plasma by means of dialysis. An increased clearance of vancomycin by high-flux hemodialysis, hemofiltration or hemoperfusion with polysulfon resin has been reported.

Symptomatic treatment.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group
Intestinal antiinfective, antibiotics, ATC code: A 07 AA 09

Mechanism of action

Vancomycin is a tricyclic glycopeptide antibiotic w hat 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(s) 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, 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:

	Susceptible	**Resistant**
Clostridium difficile[1]	≤ 2 mg/L	> 2 mg/L

[1] 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 exclusively in the faeces. During multiple dosing of 250 mg 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%.

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.

Administration of vancomycin oral solution, 2 g daily for 16 days to anephric patients with no inflammatory bowel disease, gave measurable serum levels of >0.66 μg/ml in 2 out of 5 patients. With doses of 2 g daily, concentrations of >3,100 mg/kg were found in the faeces and levels of <1 μg/ml were found in the serum of patients with normal renal function who had pseudomembranous colitis.

Following parenteral administration vancomycin is excreted renally, nearly completely as the microbiologically active substance. The serum half-life in adult patients with normal renal function has been reported to be about 4-6 hours, in children 2.2-3 hours. Impaired renal function can prolong the elimination (up to 7.5 days).

Mutagenic and tumorigenic potential: Vancomycin was only limitedly tested with regard to mutagenic effect. Tests performed so far yielded negative results. Fertility studies and long-term investigations in animals with regard to evaluate carcinogenic potential are not available.

Teratogenic potential: In teratogenic studies, where rats and rabbits received doses approximately corresponding to the human dose based on body surface (mg/m^3), 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

Polyethylene glycol 6000.

Capsule: Black iron oxide E-172, titanium dioxide E-171, yellow iron oxide E-172, Indigo carmine E-132, gelatin.

Printing ink on the capsules: Shellac, propylene glycol, sodium hydroxide, povidone, titanium dioxide E-171.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Room temperature (15-25°C). Protect from moisture.

6.5 Nature and contents of container

Unit dose blister packs of PVC/PE/PCTFE on aluminium foil.
Pack size: 28 capsules.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Xellia Pharmaceuticals ApS
Dalslandsgade 11,
2300 Copenhagen S
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PL 17815/0042

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

14/08/1996

10 DATE OF REVISION OF THE TEXT

28/01/2021