Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Vancocin Matrigel 125mg Hard Capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Hard capsule
Dark blue and brown capsules, imprinted with 3125 in red ink.

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 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.

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.

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. 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 interactions

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

Usage in 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.

Usage in nursing mothers: 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

None known.

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, agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia.			
Immune system disorders:				
Rare	Hypersensitivity reactions, anaphylactic reactions			

Ear and labyrinth disorders:				
Uncommon	Transient or permanent loss of hearing			
Rare	Vertigo, tinnitus, 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			
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.

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.

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 listed below:

HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Treatment of Overdosage
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

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 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 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

There are no preclinical data of relevance to the prescriber in addition to that summarised in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule Contents
Macrogol 6000

Capsule Shell
Gelatin
Indigo Carmine (E132)
Red iron oxide (E172)
Yellow iron oxide (E172)
Titanium Dioxide (E171)

Printing Ink
Shellac
Propylene glycol
Potassium hydroxide
Red iron oxide (E172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package

6.5 Nature and contents of container

A1/PVC/PE/Aclar blister packs of 20 capsules (2 strips of 10 capsules) and 28 capsules (4 strips of 7 capsules).

Not all pack sizes may be marketed

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements

7 MARKETING AUTHORISATION HOLDER

Flynn Pharma Limited
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Dublin 4
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8 MARKETING AUTHORISATION NUMBER

PA1226/005/001

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10 DATE OF REVISION OF THE TEXT

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