SCHEDULING STATUS

S4

1 NAME OF MEDICINE
COMAVYN 125 capsules
COMAVYN 250 capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
COMAVYN 125: Each capsule contains vancomycin hydrochloride equivalent to 125 mg vancomycin.
COMAVYN 250: Each capsule contains vancomycin hydrochloride equivalent to 250 mg vancomycin.
Sugar free. For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Hard gelatine capsules.
125 mg: COMAVYN is a white to off white congealed liquid mixture as solid mass in size '2' grey cap and pink body hard gelatine capsule.
250 mg: COMAVYN is a white to off white congealed liquid mixture as solid mass in size '0' brown cap and brown body hard gelatine capsule.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
COMAVYN capsules are indicated in patients 16 years and older for the treatment of *Clostridium difficil*e infection (CDI).

4.2 Posology and method of administration
Posology
Adults and adolescents aged 16 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.
The 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
COMAVYN capsules are not appropriate for the treatment of children under the age of 16 years or for adolescents unable to swallow the capsules.

Method of administration
For oral use.
The capsule should not be opened and should be taken with plenty of water.

4.3 Contraindications
- Hypersensitivity to vancomycin or to any of the excipients of COMAVYN (see section 6.1).
- Hearing loss
- Renal impairment
- Pregnancy and lactation
- Children younger than 16 years old.

4.4 Special warnings and precautions for use
Oral use only
COMAVYN is for oral use only and is not systemically absorbed. Orally administered COMAVYN 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 medicines.

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 medicine such as an aminoglycoside.

Drug interactions with anti-motility medicines and proton pump inhibitors
Anti-motility medicines should be avoided, and proton pump inhibitor use should be reconsidered.

Development of drug-resistant bacteria
Prolonged use of COMAVYN 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.

Paediatric population
Do not use in children under the age of 16 years old.

4.5 Interaction with other medicines and other forms of interaction
Concurrent and/or sequential systemic or topical use of other potentially ototoxic and/or nephrotoxic medicines requires careful monitoring.
Consideration should be given to discontinuing proton pump inhibitors and anti-motility medicines in line with local guidelines for treatment of *Clostridium difficile* infection.

4.6 Fertility, pregnancy and lactation
Pregnancy
COMAVYN should not be given to a pregnant woman.
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. Clinical studies showed that the potential ototoxic and nephrotoxic effects of vancomycin hydrochloride on infants were evaluated when the medicine was administered to pregnant women for serious staphylococcal infections complicating intravenous medicine 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, therefore it is not known whether it causes foetal harm.

Breastfeeding
COMAVYN is excreted in human milk. Women on treatment with COMAVYN should not breastfeed their babies. COMAVYN should therefore only be used during breastfeeding if other antibiotics have failed. In breastfed infants, disorders of the intestinal flora with diarrhoea, fungus infection and possibly sensitisation may occur. Risks of systemic effects in premature and young neonates exposed to COMAVYN in breast milk cannot be excluded due to relatively high intestinal permeability and immature elimination functions of these infants.

4.7 Effects on ability to drive and use machines
COMAVYN has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects
a. Summary of the safety profile
The absorption of COMAVYN 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.

b. Tabulated summary of adverse reactions

MedDRA System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Less frequent	Reversible neutropenia[1], agranulocytosis, eosinophilia, thrombocytopenia, pancytopenia
Immune system disorders	Less frequent	Hypersensitivity reactions, anaphylactic reactions
Ear and labyrinth disorders	Less frequent	Transient or permanent loss of hearing[3], vertigo, tinnitus, dizziness[2]
Cardiac disorders	Less frequent	Cardiac arrest
Vascular disorders	Frequent	Decrease in blood pressure
	Less frequent	Vasculitis
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea, stridor
Gastrointestinal disorders	Less frequent	Nausea, pseudomembranous enterocolitis
	Frequency unknown	Vomiting, diarrhoea
Skin and subcutaneous tissue disorders	Frequent	Flushing of the upper body (red man syndrome), exanthema and mucosal inflammation, pruritus, urticaria
	Less frequent	Exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, Linear IgA bullous dermatosis[4]
	Frequency unknown	Eosinophilia and systemic symptoms (DRESS syndrome), AGEP (Acute Generalized Exanthematous Pustulosis)
Renal and urinary disorders	Frequent	Renal insufficiency manifested primarily by increased serum creatinine and serum urea
	Less frequent	Interstitial nephritis, acute renal failure
	Frequency unknown	Acute tubular necrosis
General disorders and administration site conditions	Frequent	Phlebitis, redness of the upper body and face
	Less frequent	Drug fever, shivering, pain and muscle spasm of the chest and back muscles

c. Description of selected adverse reactions
[1] Reversible neutropenia usually starting one week or more after onset of intravenous therapy or after total dose of more than 25 g.
[2] Tinnitus, possibly preceding onset of deafness, should be regarded as an indication to discontinue treatment.
[3] Ototoxicity has primarily been reported in patients given high doses, or in those on concomitant treatment with other ototoxic medicines like aminoglycoside, or in those who had a pre-existing reduction in kidney function or hearing.
[4] If a bullous disorder is suspected, COMAVYN should be discontinued and specialised dermatological assessment should be carried out.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose
Supportive care is advised, with maintenance of glomerular filtration. COMAVYN is poorly removed by dialysis. Haemofiltration and haemoperfusion have been reported to be of limited benefit.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibiotics, 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 medicine is bactericidal for dividing micro-organisms. 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 medicine 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:

Clostridium difficile[1]	Susceptible ≤ 2 mg/l	Resistant > 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, exceed 100 mg/kg in most of the samples. No blood concentrations are detected, and urinary recovery does 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.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Capsule contents
Polyethylene glycol 6000 (E1521)
Capsule shell
Gelatine
Black iron oxide (E172)
Red iron oxide (E172)
Yellow iron oxide (E171)
Titanium dioxide (E171)

6.2 Incompatibilities
Not applicable

6.3 Shelf life
Two years

6.4 Special precautions for storage
Do not store above 25 °C. Store in the original blister in order to protect from moisture.

6.5 Nature and contents of container
COMAVYN is packed in AL-PVC/PE/ACLAR blisters containing 4 capsules, 10 capsules, 12 capsules or 14 capsules per blister pack in an outer carton. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements

7 HOLDER OF CERTIFICATE OF REGISTRATION
Strides Pharma SA (Pty) Ltd.
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Building 2
Midrand
South Africa
1686

8 REGISTRATION NUMBER(S)
COMAVYN 125: 53/20.1.1/0584
COMAVYN 250: 53/20.1.1/0585

9 DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION
15 December 2020

10 DATE OF REVISION OF THE TEXT
To follow

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