SCHEDULING STATUS
S4

PROPRIETARY NAME AND DOSAGE FORM

ZENILID 600 mg film-coated tablets

COMPOSITION

Active ingredient

Each film-coated tablet contains 600 mg linezolid.

Inactive ingredients

Croscarmellose sodium, lactose monohydrate, magnesium stearate, Opadry white (containing hypromellose, polyethylene glycol and titanium dioxide) and povidone.
Contains sugar: lactose.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Linezolid is a synthetic antimicrobial medicine of the oxazolidinone class of antibiotics. It is active against aerobic Gram-positive organisms and has limited activity against most aerobic or anaerobic Gram-negative organisms. Linezolid has bacteriostatic activity against staphylococci and enterococci and has bactericidal activity against streptococci.

It selectively inhibits bacterial protein synthesis by binding to the P site of the ribosomal subunit which in turn prevents the formation of the larger ribosomal complex that initiates protein synthesis. *In vitro* studies have shown that resistance of organisms to linezolid occurs as a result of slow point mutations of the 23S ribosomal RNA of the organisms.

Resistant organisms:

- *Haemophilus influenzae, Enterobacteriaceae, Neisseria* species and *Pseudomonas* species.

There is no cross-resistance between **ZENILID 600 mg** and other classes of antibiotics, (e.g. aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol).

Pharmacokinetic properties:

The aqueous solubility of linezolid is approximately 3 mg/mL and is independent of pH between pH 3 to 9.

Absorption:

Linezolid is well absorbed after oral administration and is not affected by concomitant food intake. Peak serum concentrations are reached within 1 - 2 hours after a single dose of 600 mg and remains at a steady state with dosing every 12 hours. Absolute bioavailability is 100 %.

Distribution:

Linezolid distributes widely to well perfused tissues and is 31 % protein bound. The volume of distribution at steady state averages approximately 40 - 50 litres in healthy adults.

Metabolism:

Linezolid is broken down by non-enzymatic oxidation to hydroxyethyl glycine derivatives and aminoethoxyacetic acid.

Elimination:

Under steady state conditions 80 % of linezolid is excreted in the urine and 10 % of the administered dose appears as oxidation products in the faeces. The elimination half-life of the parent medicine is averaged between 5 - 7 hours.

Special populations:

Elderly patients:
Serum concentrations are not significantly altered in patients aged 65 years and older.

Renal insufficiency:
The serum concentrations and half-life of the linezolid parent compound are not altered by renal insufficiency. The clinical significance of this is unknown and no dose adjustments for patients with mild, moderate or severe renal insufficiency are currently required. Dialysis eliminates linezolid and its breakdown products, therefore the dose should be administered after dialysis treatment.

Hepatic impairment:
Due to the metabolism of linezolid by a non-enzymatic process, hepatic impairment is not expected to alter the metabolism and dose adjustments in such patients are not required.

Paediatric patients:
There is wider inter-patient variability in the clearance of linezolid and the systemic medicine exposure (AUC) across all paediatric patient age groups when compared to adult patients.

INDICATIONS

ZENILID 600 mg is indicated for the treatment of patients with the following infections caused by susceptible strains of the designated microorganisms (see **PHARMACOLOGICAL ACTION**):

- **Vancomycin-resistant *Enterococcus faecium* infections:** including cases with concurrent bacteraemia.
- **Nosocomial pneumonia:** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant *S. pneumoniae* (MDRSP) strains). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.
- **Complicated skin and skin structure infections:** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*. **ZENILID 600 mg** has not been studied in the treatment of decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.
- **Uncomplicated skin and skin structure infections:** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains) or *Streptococcus pyogenes*.

• **Community-acquired pneumonia:** caused by *Streptococcus pneumoniae* (including multi-drug resistant *S. pneumoniae* (MDRSP) strains), including cases with concurrent bacteraemia, or *Staphylococcus aureus* methicillin-susceptible and -resistant strains).

CONTRAINDICATIONS

• Hypersensitivity to linezolid or any of the other ingredients of **ZENILID 600 mg** (see **COMPOSITION**).
• Patients on monoamine oxidase inhibitors.
• Pregnancy and lactation (see **PREGNANCY AND LACTATION**).

WARNINGS AND SPECIAL PRECAUTIONS

Antibiotics associated diarrhoea:

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has been reported in association with the use of nearly all antibiotics including linezolid and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of linezolid. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including linezolid, should be discontinued and adequate therapeutic measures should be initiated immediately. Medicines inhibiting peristalsis are contraindicated in this situation.

Pseudomembranous colitis:

Pseudomembranous colitis must be considered if a patient presents with diarrhoea after the use of **ZENILID 600 mg**. It may range in severity from mild to life-threatening. The onset of diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with **ZENILID 600 mg** may indicate the appearance of pseudomembranous colitis. Suspicion of pseudomembranous colitis requires immediate cessation of treatment with appropriate specific antibiotic therapy effective against *Clostridium difficile*.

MAO Inhibitors:

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI); however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medicines which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible.

Myelosuppression:

Myelosuppression can occur in patients who receive treatment with **ZENILID 600 mg** for longer than 10 - 14 days. Platelet counts should be monitored in patients presenting with myelosuppresion, including anaemia, leukopenia, pancytopenia and thrombocytopenia, patients who receive other medicines causing bone marrow depression, patients with chronic infections and patients who are receiving concurrent antibiotic treatment. Discontinuation of treatment with **ZENILID 600 mg** should be considered in patients with worsening myelosuppresion. Medical treatment is required and weekly blood count monitoring is recommended.

Peripheral or optic neuropathy:

Peripheral neuropathy, optic neuropathy and lactic acidosis can occur in patients receiving long-term (e.g. > 8 weeks) treatment with **ZENILID 600 mg**. This may be as a result of the effect of **ZENILID 600 mg** on mitochondria. **ZENILID 600 mg** is not recommended for long-term use, as effects have not always been reversible.

If symptoms of visual impairment such as changes in colour vision, blurred vision, loss of vision or visual field defects, burning, numbness, tingling, painful sensations, weakness in the arms, hands, legs or feet, unsteadiness or awkwardness occur while taking **ZENILID 600 mg**, medical evaluation is required.

Superinfections:

The use of antibiotics may promote the overgrowth of non-susceptible organisms. Should a superinfection occur during **ZENILID 600 mg** treatment, appropriate measures should be taken.

ZENILID 600 mg should be given along with appropriate antibacterial cover for Gram-negative organisms in patients with mixed Gram-positive and Gram-negative infections.

Lactic acidosis:

Lactic acidosis may occur in patients taking **ZENILID 600 mg**. If recurrent signs of nausea, vomiting, unexplained acidosis or a low bicarbonate level occur, it may be indicative of lactic acidosis and medical evaluation is required.

Convulsions:

Patients with a history of seizures or presenting with seizure risk factors, may be predisposed to having convulsions when taking **ZENILID 600 mg**.

Serotonin syndrome:

Serotonin syndrome has been reported in patients receiving concomitant serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), while taking **ZENILID 600 mg** (see **INTERACTIONS**).

The safety and efficacy of **ZENILID 600 mg** when taken for periods longer than 28 days have not been established. **ZENILID 600 mg** has not been studied.

Due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms, healthcare practitioners should carefully consider alternatives before starting treatment with **ZENILID 600 mg** in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to **ZENILID 600 mg**. Therapy may be instituted empirically while awaiting results of these tests. Antimicrobial therapy should be adjusted accordingly, once these results become available.

Effects on ability to drive and use machinery:

No effects on the ability to drive a vehicle and the use of machinery have been reported. Patients should be warned about the potential for dizziness or symptoms of visual impairment, like blurred vision, whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs.

Lactose monohydrate:

ZENILID 600 mg contains lactose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take **ZENILID 600 mg**.

INTERACTIONS

- **ZENILID 600 mg** is a reversible, non-selective monoamine oxidase inhibitor (MAOI) and has the potential to interact with adrenergic and serotonergic medicines. Enhanced pressor activity has been reported in patients taking **ZENILID 600 mg** in combination with phenylpropanolamine or pseudoephedrine and doses of dopamine or epinephrine (adrenaline) should be reduced.
- Tyramine containing foods (e.g. matured cheese, yeast extracts, undistilled alcoholic beverages and fermented soybean products such as soy sauce) may cause a significant pressor response if consumed in more than 100 mg is consumed concurrently with **ZENILID 600 mg**.
- Serotonin syndrome has been reported when **ZENILID 600 mg** is used concurrently with serotonin reuptake inhibitors (antidepressants) and dextromethorphan (cough suppressant) (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- The use of **ZENILID 600 mg** with bone marrow suppressants may increase the thrombocytopenic and leucopenic effects of these medicines and weekly monitoring and blood counts are recommended.
- Medicines causing induction of hepatic enzymes (e.g. rifampicin) may cause decreases in **ZENILID 600 mg** exposure.

PREGNANCY AND LACTATION

The use of **ZENILID 600 mg** during pregnancy and lactation is contraindicated (see **CONTRAINDICATIONS**).
Safety in pregnancy and lactation has not been established.

Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans; possible effects of linezolid on the human male reproductive system are not known.

DOSAGE AND DIRECTIONS FOR USE

ZENILID 600 mg tablets may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as **ZENILID 600 mg** has an oral bioavailability of approximately 100 %.

ZENILID 600 mg may be taken with or without food.

The recommended dosage for **ZENILID 600 mg** is described below:

Adults and adolescents (12 years and older):

Infections (including those associated with concurrent bacteraemia)	**Twice daily dosage**	**Duration of treatment**
Community-acquired pneumonia, including concurrent bacteraemia	600 mg orally	10 - 14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia		
Skin and soft tissue infections, including concurrent bacteraemia	400 mg to 600 mg orally	
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg orally	14 - 28 consecutive days

Elderly patients:

No dose adjustment of **ZENILID 600 mg** is necessary.

Patients with impaired renal function:

There is no evidence of parent compound accumulation in patients with any degree of renal insufficiency.

Patients with mild-to-moderate renal insufficiency i.e. creatine clearance (CL_{CR}) > 30 mL/min:

No dose adjustment of **ZENILID 600 mg** is necessary.

Patients with severe renal insufficiency i.e. CL_{CR} ≤30 mL/min:

Dosage should not be reduced in these patients. However, there is evidence that the primary metabolites of **ZENILID 600 mg** accumulate in patients with severe renal insufficiency. The clinical significance of this has not been established.

ZENILID 600 mg should be taken after haemodialysis in patients receiving such treatment.

Patients with impaired hepatic function:

No dose adjustment is necessary.

SIDE EFFECTS

Blood and the lymphatic system disorders:

Frequent: Myelosuppresion, anaemia, leukopenia, pancytopenia and thrombocytopenia. Increased: neutrophils or eosinophils. Decreased: haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.

Less frequent: Eosinophilia and neutropenia. Increased: reticulocyte count. Decreased: neutrophils.

Immune system disorders:

Less frequent: Bullous skin eruptions including Stevens-Johnson syndrome, angioedema.

Metabolism and nutrition disorders:

Less frequent: Lactic acidosis and hyperglycaemia.

Psychiatric disorders:

Less frequent: Insomnia.

Nervous system disorders:

Less frequent: Headache, hypoaesthesia, paraesthesia, peripheral neuropathy, convulsions and serotonin syndrome.

Eye disorders:

Less frequent: Optic neuropathy, blurred vision, loss of vision, optic neuritis and visual field defects.

Ear and labyrinth disorders:

Less frequent: Tinnitus.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Increased serum creatinine phosphokinase.

Vascular disorders:

Less frequent: Dizziness, hypertension and hypotension, transient ischaemic attacks.

Gastrointestinal disorders:

Frequent: Diarrhoea, pseudomembranous colitis, nausea, vomiting, constipation, metallic taste, oral candidiasis, abdominal pain and cramps or distension, taste disturbances.

Less frequent: Dry mouth, dyspepsia, gastritis, increased thirst, pancreatitis and tongue or teeth discolouration.

Skin and subcutaneous tissue disorders:

Less frequent: Dermatitis, diaphoresis, pruritus, rash and urticaria, alopecia.

Renal and urinary disorders:

Less frequent: Polyuria.

Reproductive system and breast disorders:

Frequent: Vaginal candidiasis.

Less frequent: Vulvovaginal disorder and vaginitis.

General disorders and administrative site conditions:

Frequent: Fever, candidiasis or fungal infections.

Less frequent: Fatigue and chills.

Investigations:

Frequent: Increased: bilirubin, AST, ALT, LDH, alkaline phosphatase, blood urea, creatine kinase, lipase, amylase or non-fasting glucose. Decreased: total protein, albumin, sodium, calcium. Increased or decreased: potassium or bicarbonate.

Less frequent: Increased: creatinine, sodium, calcium. Decreased: non-fasting glucose. Increased or decreased: chloride.

KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT

There are no reported cases of overdose with **ZENILID 600 mg**. Signs of toxicity in rats following doses of 3 000 mg/kg/day linezolid were decreased activity and ataxia whilst dogs treated with 2 000 mg/kg/day experienced vomiting and tremors.

Treatment is supportive with maintenance of glomerular filtration. Approximately 30 % of linezolid is removed by 3 hours of haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion.

IDENTIFICATION

White to off-white, oval, biconvex film-coated tablets, with “G44” debossed on one side and “600” on the other side.

PRESENTATION

White PVC/ACLAR-aluminium blister strips packed into an outer carton.

Pack sizes: 10 film-coated tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C.
Do not remove from outer carton until required for use.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

50/20.1.1/0001

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