SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

Linezolid Teva 600 (film-coated tablets)

COMPOSITION:

Linezolid Teva 600: Each film-coated tablet contains 600 mg linezolid.

Excipients:

Tablet core: Croscarmellose sodium, crospovidone, hydroxypropylcellulose, lactose monohydrate, magnesium stearate, maize starch, Starlac® (composed of lactose monohydrate and maize starch).

Film-coating: Opadry Y1-7000H White consisting of hypromellose, macrogol 400, titanium dioxide.

Contains lactose monohydrate.

PHARMACOLOGICAL CLASSIFICATION:

A 20.1.1 Broad and medium spectrum antibiotic

PHARMACOLOGICAL ACTION:

Pharmacodynamic properties:

Linezolid is a synthetic antibacterial agent of the oxazolidinone class of antibiotics.

Through binding to the P site of the 50S ribosomal subunit of the bacteria linezolid selectively inhibits bacterial protein synthesis and prevents the formation of a functional 70S-initiation complex that is essential to the translation process.

As a result of its mechanism of action linezolid has activity against strains that are resistant to multiple other agents including penicillin-resistant strains of *S. pneumonia;* methicillin-resistant, vancomycin-intermediate, and vancomycin-resistant strains of staphylococci; and vancomycin-resistant strains of enterococci.

Inherently resistant organisms:

Haemophilus influenzae	*Neisseria* species
Enterobacteriaceae	*Pseudomonas* species

Resistance:

There is no cross-resistance between linezolid and these classes of medicines such as the aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifampicins, streptogramins, tetracyclines and chloramphenicol.

As multiple copies of 23S rRNA genes are present in bacteria, resistance generally requires mutations in two or more copies. Resistance to linezolid develops slowly via multiple step mutations in 23S ribosomal RNA and occurs at frequencies of less than 1×10^{-9} to 1×10^{-11} as illustrated by *in vitro* studies.

Pharmacokinetic properties:

Linezolid Teva 600 primarily contains the biologically active ingredient linezolid that is metabolised to form inactive metabolites.

Absorption:

Following oral administration, linezolid is well absorbed and absorption is not affected by food.

Maximum plasma concentrations are reached within 2 hours after a single 600 mg dose and absolute bioavailability is approximately 100 %.

Distribution:

Linezolid distributes widely to well perfused issues and has a volume of distribution average at steady-state of about 40 to 50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31 %.

Metabolism:

The morpholine ring of linezolid is metabolised by a non-enzymatic metabolic oxidation process to two inactive open-ring carboxylic acid derivatives.

The hydroxyethyl glycine metabolite (B) is the predominant human metabolite and the amino ethoxy acetic acid metabolite (A) is less abundant.

Linezolid is not markedly metabolised by cytochrome P450 (CYP) isoenzymes *in vitro* and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4).

Linezolid does not significantly induce major cytochrome P450 isoenzymes in rats and does not induce human CYP2C9.

Elimination:

Approximately 80 % of the dose of linezolid appears in the urine as metabolite B (40 %), parent substance (30-35 %) and metabolite A (10 %) under steady-state conditions.

The $T_{1/2}$ of the parent substance average at about 5-7 hours.

Non-renal clearance accounts for approximately 65 % of the total clearance of linezolid.

Special populations:

Elderly:

In elderly patients aged 65 and over the pharmacokinetics of linezolid is not significantly altered.

Renal insufficiency:

As linezolid clearance is independent of creatinine clearance it is not necessary to adjust the dose in patients with mild or moderate renal insufficiency.

There is evidence that the primary metabolites of linezolid accumulate in patients with severe renal insufficiency (i.e. $CL_{CR} < 30$ ml/min).

The clinical significance of this is not known.

Approximately 30 % of linezolid and its breakdown products are eliminated during 3 hours of haemodialysis (beginning 3 hours after administration). Linezolid Teva 600 should therefore be given after dialysis in patients undergoing haemodialysis

Hepatic insufficiency:

The pharmacokinetics of linezolid is not altered in patients with mild to moderate hepatic insufficiency. Adjustment of dosage is therefore, not required in such patients.

The pharmacokinetics of linezolid in patients with severe hepatic insufficiency has not been evaluated.

INDICATIONS:

Linezolid Teva 600 is indicated for the treatment of patients with the following infections caused by susceptible strains of micro-organisms.

- **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[1]) strains). If the documented or presumptive pathogens include Gram-negative organisms combination therapy may be clinically indicated.
- **Complicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes,* or *Streptococcus agalactiae.* If the documented or presumptive pathogens include Gram-negative organisms combination therapy may be clinically indicated.
- **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multi-drug resistant *S. pneumoniae* (MDRSP[1]) strains), including cases with concurrent bacteraemia, or *Staphylococcus aureus* (methicillin-susceptible and -resistant strains).

1 MDRSP, Multi-drug resistant *Streptococcus pneumonia* includes isolates previously known as penicillin-resistant *Streptococcus pneumonia*, and are strains resistant to two or more of the following antibiotics: penicillin, second generation cephalosporins, macrolides, tetracyclines, and trimethoprim/ sulfamethoxazole.

CONTRAINDICATIONS:

The use of Linezolid Teva 600 is contraindicated in

- Patients who have known hypersensitivity to linezolid or any excipients in Linezolid Teva 600.
- Patients taking any medicine which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks after discontinuation of taking any such medicine.
- Linezolid Teva 600 should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medications:
  - Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
  - Patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), Serotonin-norepinephrine reuptake inhibitors (SNRIs), direct and indirect acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressor agents (e.g. epinephrine (adrenaline), norepinephrine (noradrenaline)), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.
- Pregnancy and lactation (see ‘’Pregnancy and lactation’’).

WARNINGS AND SPECIAL PRECAUTIONS:

Antibiotic-associated diarrhoea and colitis

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile* –associated diarrhoea, has been reported in association with the use of Linezolid Teva 600, and may range in severity from mild diarrhoea to fatal colitis. In antibiotic-associated colitis, treatment with Linezolid Teva 600 should be discontinued. Appropriate therapy should be instituted. It is therefore important to consider this diagnosis in patients who present with diarrhoea subsequent to the use of Linezolid Teva 600. In cases of suspected or verified antibiotic-associated colitis, discontinuation of linezolid may be warranted.

Appropriate management measures should be instituted. Medicines inhibiting gut motility/peristalsis are contraindicated in this situation.

Superinfection

Overgrowth of non-susceptible organisms such as *C.difficile* may occur with the use of antibiotics. *C.difficile* associated diarrhoea should be considered in all patients presenting with diarrhoea after use of Linezolid Teva 600. Appropriate measures should be taken in the event of super infection occurring.

Serotonin syndrome

Serotonin syndrome associated with the co-administration of Linezolid Teva 600 and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of Linezolid Teva 600 and serotonergic agents is therefore contraindicated (see "Interactions"). If signs or symptoms of Serotonin syndrome occur the medical practitioner should consider discontinuing either one or both medicines; if the concomitant serotonergic medicine is withdrawn, discontinuation symptoms can occur.

Myelosuppression

Myelosuppression (including anaemia, leukopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid, as in Linezolid Teva 600. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with Linezolid Teva 600 may be at greater risk of experiencing blood dyscrasias than younger patients.

Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis. Therefore, close monitoring of blood counts is recommended in patients who have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 10-14 days of therapy. Linezolid Teva 600 should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible.

If significant myelosuppression occurs during Linezolid Teva 600 therapy, treatment should be stopped unless it is considered absolutely necessary to continue therapy, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented.

In addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count.

Cases of sideroblastic anaemia have been reported.

Lactic acidosis

Lactic acidosis has been reported with the use of Linezolid Teva 600. Patients who develop signs and symptoms of metabolic acidosis including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level, or hyperventilation while receiving Linezolid Teva 600 should receive immediate medical attention. If lactic acidosis occurs, careful consideration should be given to treatment continuation with Linezolid Teva 600.

Mitochondrial dysfunction

Linezolid inhibits mitochondrial protein synthesis. Adverse events, such as lactic acidosis, anaemia and neuropathy (optic and peripheral), may occur as a result of this inhibition; these events are more common when Linezolid Teva 600 is used longer than 28 days.

Peripheral and optic neuropathy

Peripheral neuropathy, as well as optic neuropathy and optic neuritis sometimes progressing to loss of vision, have been reported in patients treated with Linezolid Teva 600; these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days.

All patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect. In such cases, prompt evaluation is recommended

with referral to an ophthalmologist as necessary. If any patients are taking Linezolid Teva 600 for longer than the recommended 28 days, their visual function should be regularly monitored.

If peripheral or optic neuropathy occurs, the continued use of Linezolid Teva 600 should be reconsidered.

There may be an increased risk of neuropathies when Linezolid Teva 600 is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis.

Convulsions

Convulsions have been reported to occur in patients when treated with Linezolid Teva 600. In most of these cases, a history of seizures or risk factors for seizures was reported. Patients should be advised to inform their medical practitioner if they have a history of seizures.

Porphyria

Caution is advised in patients with porphyria, as Linezolid Teva 600 is possibly porphyrinogenic.

Use with tyramine-rich foods

Patients should be advised against consuming large amounts of tyramine rich foods (see “Interactions”).

Special populations

Caution is advised when used in patients with severe renal and/or hepatic insufficiency.

Other

When Linezolid Teva 600 is given as monotherapy patients with mixed (Gram-negative and Gram-positive) infections are at higher risk of mortality; therefore Linezolid Teva 600 must be administered with appropriate antibacterial cover for Gram-negative organisms in these patients.

Prescribers should carefully consider alternatives before starting Linezolid Teva 600 treatment in the outpatient setting due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms.

In order to isolate and identify the causative organisms and to determine linezolid activity against these organisms, appropriate specimens for bacteriological examination should be obtained.

Therapy may be instituted empirically while awaiting results of these tests.

Once these results become available, antimicrobial therapy should be adjusted accordingly.

The safety and efficacy of Linezolid Teva 600 have not been established when administered for more than 28 days and alternative therapy should be considered.

Effects on ability to drive and use machinery

Patients should be warned about the potential for dizziness or symptoms of visual impairment (see "Warnings and special precautions" and "Side effects") whilst receiving Linezolid Teva 600 and should be advised not to drive or operate machinery if any of these symptoms occurs.

Linezolid Teva 600 contains lactose and should not be administered to patients with rare hereditary problems, or a history of lactose/galactose intolerance, Lapp lactose deficiency or glucose-galactose malabsorption.

INTERACTIONS:

Monoamine oxidase inhibitors

Linezolid Teva 600 is a monoamine inhibitor (MAOI). Linezolid Teva 600 produces, reversible enhancement of the pressor responses induced by pseudoephedrine and phenyl-propanolamine hydrochloride. Thus, the potential for interaction with sympathomimetic or adrenergic agents should be considered and doses of compounds, such as dopamine or epinephrine (adrenalin), should be titrated to achieve the desired response.

Potential serotonergic interactions

Linezolid Teva 600 has the potential for interaction with serotonergic agents, serotonin effects (e.g. confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) may occur in patients receiving linezolid and dextromethorphan.

Medicine metabolised by cytochrome P450

Linezolid Teva 600 does not induce or inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4) as it is not detectably metabolised by the cytochrome P450 (CYP) enzyme system. No CYP450-induced medicine interactions are therefore expected.

Use with tyramine-rich foods

It is necessary to avoid ingesting large amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

Opioid analgesics (pethidine)

Serotonin syndrome can occur when Linezolid Teva 600 and pethidine are taken together; this is attributed to the inhibitory action of linezolid on monoamine oxidase. The symptoms resolve when the pethidine is stopped.

Potential interactions producing elevation of blood pressure

Co-administration of Linezolid Teva 600 with either pseudoephedrine or phenylpropanolamine results in mean increases in systolic blood pressure. It is recommended that doses of medicines with a vasopressive action, including dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered with Linezolid Teva 600.

Rifampicin

Rifampicin decreases the linezolid C_{max} and AUC by a mean 21 % and a mean 32 % respectively. The mechanism of this interaction and its clinical significance are unknown.

During concurrent treatment of other bone marrow depressants and Linezolid Teva 600 it is recommended that complete blood count be monitored weekly as leukopenic and / or thrombocytopenic effects of these medicines may be increased.

PREGNANCY AND LACTATION:

The use of Linezolid Teva 600 is contraindicated in pregnancy and lactation, as safety has not been demonstrated.

DOSAGE AND DIRECTIONS FOR USE:

Linezolid Teva 600 tablets may be used as initial therapy.

Linezolid Teva 600 tablets may be taken with or without food (see "*Pharmacokinetic properties")*.

The recommended Linezolid Teva 600 dosage should be administered orally as described in the tables below.

Adult and adolescent (12 years and older) patients:

Infections (including those associated with concurrent bacteraemia)	**Twice daily dosage and route of administration**	**Duration of treatment**
Community-acquired pneumonia, including concurrent bacteraemia Nosocomial pneumonia, including concurrent bacteraemia	600 mg orally	10-14 consecutive days
Severe Skin and soft tissue infections, including concurrent	600 mg orally	

bacteraemia		
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg orally	14-28 consecutive days

Elderly patients:

No dose adjustment is necessary.

Patients suffering from impaired renal function:

Caution is advised when used in patients with severe renal insufficiency.

Patients with hepatic function impairment:

No adjustment of dose is necessary.

Caution is advised when used in patients with severe hepatic insufficiency.

SIDE EFFECTS:

The most frequently reported side effects are headache, diarrhoea, nausea, vomiting, metallic taste, abnormal liver function tests and vaginal moniliasis.

Infections and infestations:

Frequent: Candidiasis, oral candidiasis, vaginal candidiasis or fungal infection.

Less frequent: Antibiotic-associated colitis, including pseudomembranous colitis and *C.difficile* associated diarrhoea, vaginitis.

Frequency not known: Antibiotic associated colitis, *Clostridium difficile* associated diarrhoea (CDAD), pseudomembranous colitis (which may be fatal; see ‘’Warnings and special precautions’’).

Blood and the lymphatic system disorders:

Less frequent: Anaemia, eosinophilia, leukopenia, neutropenia, thrombocytopenia, pancytopenia.

Frequency not known: Myelosuppression, sideroblastic anaemia.

Immune system disorders:

Frequency not known: Anaphylaxis, hypersensitivity reactions, angioedema.

***Metabolism and nutrition disorders*:**

Less frequent: Increased serum creatine phosphokinase, hyperglycaemia.

Frequency not known: Lactic acidosis, hyponatraemia.

Psychiatric disorders:

Less frequent: Insomnia.

***Nervous system disorders*:**

Frequent: Headache.

Less frequent: Dizziness, hypoaesthesia, paraesthesia.

Frequency not known: Serotonin syndrome, convulsions, peripheral neuropathy.

***Eye disorders*:**

Less frequent: Blurred vision.

Frequency not known: Optic neuropathy, optic neuritis, loss of vision, changes in visual acuity, changes in colour vision, changes in visual field defect (see ‘’Warnings and special precautions’’).

***Ear and labyrinth disorders*:**

Less frequent: Tinnitus.

***Cardiac disorders*:**

Less frequent:

Dysrhythmia (tachycardia).

***Vascular disorders*:**

Less frequent: Hypertension, hypotension, transient ischaemic attacks.

***Gastrointestinal disorders*:**

Frequent: Taste perversion (metallic taste), abdominal pain, cramps or distension, diarrhoea, nausea, vomiting.

Less frequent: Constipation, dry mouth, dyspepsia, gastritis, increased thirst, pancreatitis, stomatitis, tongue discolouration or disorder, dysgeusia, glossitis, loose stools.

Frequency not known: Superficial tooth discolouration

***Hepato-biliary disorders*:**

Frequent: Abnormal liver function test (see ‘’Investigations’’).

***Skin and subcutaneous tissue disorders*:**

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

Frequency not known: Bullous disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis, alopecia.

***Renal and urinary disorders*:**

Less frequent: Polyuria, renal failure.

***Reproductive system and breast disorders*:**

Less frequent: Vulvovaginal disorder.

***General disorders and administrative site disorders*:**

Less frequent: Chills, fatigue, fever, increased thirst, phlebitis/ thrombophlebitis.

***Investigations*:**

Frequent:

Chemistry: Increased total 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.

Haematology: Increased neutrophils or eosinophils, decreased haemoglobin, haematocrit or red blood cell count, increased or decreased platelet or white blood cell counts.

Less frequent:

Chemistry: Increased creatinine, sodium, calcium, decreased non-fasting glucose, increased or decreased chloride.

Haematology: Increased reticulocyte count; decreased neutrophils.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

Refer to ‘’Side effects’’.

In the event of over dose supportive care is advised together with maintenance of glomerular filtration.

Approximately 30 % of linezolid dose is removed during 3 hours of haemodialysis, but no data are available for the removal of Linezolid Teva 600 by peritoneal dialysis or haemoperfusion.

IDENTIFICATION:

A white, film-coated modified capsule shaped tablet, debossed with “600” on one side. The other side is scored.

PRESENTATION:

- PVC / PVdC transparent and Aluminium blister packs
- OPA/Aluminium/PVC and Aluminium (push through) blister packs

The blister strips are packed in cardboard boxes. Pack sizes: 10, 20, 28, 30, 60, 90, 100 tablets per outer carton or hospital pack of 50 x 1.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

Keep the tablets in the blister strip and the blister strip in the outer carton until required for use.

KEEP ALL MEDICINE OUT OF REACH AND SIGHT OF CHILDREN.

REGISTRATION NUMBER:

48/20.1.1/1315

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

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