PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ELTURIN 600 (Film-coated tablets)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg linezolid.

Sugar free.

Excipients:

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

White to off-white, capsule shaped, biconvex film-coated tablets with deep score on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ELTURIN 600 are indicated for the treatment of patients with the following infections caused by susceptible strains of the designated micro-organisms. **ELTURIN 600** is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy must be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see section 4.4).

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).

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

Due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with **ELTURIN 600** in the outpatient setting.

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

4.2 Posology and method of administration

ELTURIN 600 may be used as initial therapy.

The recommended dosage should be administered as described in table below:

Adult and adolescent (12 years and older) patients:

Infections (including those associated with concurrent bacteraemia	**Dosage**	**Duration of treatment**
Community-acquired pneumonia, including concurrent bacteraemia	600 mg every 12 hours	10-14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia		
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg every 12 hours	14-28 consecutive days

Special populations:

Elderly patients: No dose adjustment is necessary.

Patients with renal insufficiency: No dose adjustment is required.

Patients with severe renal insufficiency (i.e. CL_{CR}< 30 mL/min): No dose adjustment is required. Due to the unknown clinical significance of higher exposure (up to 10 fold) to the two primary metabolites of linezolid as contained in **ELTURIN 600,** in patients with severe renal insufficiency, **ELTURIN 600** should be used with special caution in these patients.

As approximately 30 % of a **ELTURIN 600** dose is removed during 3 hours of haemodialysis, **ELTURIN 600** should be given after dialysis in patients receiving such treatment. The primary metabolites of **ELTURIN 600** are removed to some extent by hemodialysis, but the concentrations of these metabolites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore, **ELTURIN 600** should be used with special caution in patients with severe renal insufficiency who are undergoing dialysis. To date, there is no experience of **ELTURIN 600** administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than hemodialysis).

Patients with hepatic insufficiency: No dose adjustment is required. However, there are limited clinical data and it is recommended that **ELTURIN 600** should be used in such patients with caution.

Method of administration:

Oral use.

ELTURIN 600 may be taken with or without food.

Paediatric population

The ELTURIN 600 is not suitable for children under 12 years of age.

4.3 Contraindication

ELTURIN 600 formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any excipients listed in section 6.1.

Monoamine Oxidase Inhibitors

ELTURIN 600 should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within two weeks of taking any such medicines.

Potential interactions producing elevation of blood pressure

ELTURIN 600 should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medicines:

- Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, hyperthyroidism, bipolar depression, schizoaffective disorder, acute confusional states.

- Patients taking any of the following medicines: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), directly and indirectly acting sympathomimetic medicines (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive medicines (e.g. epinephrine (adrenaline), norepinephrine (noradrenaline)), dopaminergic medicines (e.g. dopamine, dobutamine), pethidine or buspirone (see section 4.5).

Breastfeeding

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breast feeding should be discontinued prior to and throughout administration.

Potential serotonergic interactions

ELTURIN 600 should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medicines: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone (see section 4.5).

4.4 Special warnings and precautions for use

Antibiotic-associated diarrhoea and colitis.

Pseudomembranous colitis has been reported with **ELTURIN 600**, and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of **ELTURIN 600**.

Clostridium difficile associated diarrhoea (CDAD) has been reported with **ELTURIN 600**, and may range in severity from mild diarrhoea to fatal colitis. Treatment with **ELTURIN 600** alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines.

Myelosuppression

Reversible myelosuppression (anemia, thrombocytopenia, leukopenia and pancytopenia) that may be dependent on duration of therapy has been reported in some patients receiving **ELTURIN 600**. Monitoring of complete blood counts should be considered for patients who are at increased risk for bleeding, who have pre-existing myelosuppression, who receive concomitant medicines that may decrease haemoglobin levels or platelet count or function, or who receive **ELTURIN 600** for more than 2 weeks.

Elderly patients treated with **ELTURIN 600** may be at greater risk of experiencing blood dyscrasias than younger patients.

If significant myelosuppression occurs during **ELTURIN 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.

Peripheral and optic neuropathy

Peripheral neuropathy and optic neuropathy have been reported in patients treated with **ELTURIN 600**. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with **ELTURIN 600** for less than 28 days.

If symptoms of visual impairment appear, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking **ELTURIN 600** for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with **ELTURIN 600**. If peripheral or optic neuropathy occurs, discontinuation of ELTURIN 600 should be considered.

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

Lactic acidosis

Lactic acidosis has been reported with the use of **ELTURIN 600**. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving **ELTURIN 600** should receive immediate medical attention.

Convulsions

Convulsions have been reported to occur in patients when treated with **ELTURIN 600**. In some of these cases, a history of seizures or risk factors for seizures were reported.

Gram-negative pathogens and catheter-related bloodstream infections

ELTURIN 600 has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected. **ELTURIN 600** should be used with special caution in patients at high risk for life threatening systemic infections, such as those with infections related to central venous catheters in intensive care units. **ELTURIN 600** is not approved for the treatment of patients with catheter-related bloodstream infections.

Superinfection

The use of antibiotics may result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of **ELTURIN 600** and serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of **ELTURIN 600** and serotonergic medicines is therefore contraindicated (see section 4.3), except where administration of **ELTURIN 600** and concomitant serotonergic medicines is essential. In those cases patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur medical practitioners should consider discontinuing either one or both medicines; if the concomitant serotonergic medicine is withdrawn, discontinuation symptoms can occur.

Use with tyramine-rich foods

Patients should be advised against consuming large amounts of tyramine-rich foods (see section 4.5).

Other

The safety and effectiveness of **ELTURIN 600** when administered for periods longer than 28 days have not been established.

ELTURIN 600 has not been studied in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

ELTURIN 600 should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk.
It is recommended that **ELTURIN 600** should be used in patients with severe hepatic insufficiency only when the anticipated benefit is considered to outweigh the theoretical risk.

4.5 Interaction with other medicines and other forms of interaction

ELTURIN 600 is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Clinical studies have shown that it produces a mild reversible enhancement of the pressor responses induced by pseudoephedrine and phenylpropanolamine hydrochloride. Thus, the potential for interaction with sympathomimetic or adrenergic medicines should be considered and doses of compounds, such as dopamine or epinephrine (adrenaline), should be titrated to achieve the desired response.

Spontaneous reports of serotonin syndrome associated with the co-administration of **ELTURIN 600** and serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported.

Where administration of **ELTURIN 600** and concomitant serotonergic medicines is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur medical practitioners should consider discontinuation of either one or both medicines. If the concomitant serotonergic medicine is withdrawn, discontinuation symptoms can be observed.

In healthy volunteers, co-administration of rifampicin with **ELTURIN 600** resulted in a 21 % decrease in **ELTURIN 600** C_{max} and a 32 % decrease in **ELTURIN 600** AUC. The mechanism of this interaction and its clinical significance are unknown.

Although **ELTURIN 600** has the potential for interaction with serotonergic medicines, no serotonin effects (e.g. confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) were observed in subjects receiving **ELTURIN 600** and dextromethorphan.

Use with tyramine-rich food

No significant pressor response was observed in subjects receiving both **ELTURIN 600** and less than 100 mg tyramine. This suggests that it is only 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).

Warfarin

When warfarin was added to **ELTURIN 600** therapy at steady-state, there was a 10 % reduction in mean maximum INR on co-administration with a 5 % reduction in AUC INR. There are insufficient data from patients who have received warfarin and **ELTURIN 600** to assess the clinical significance, if any, of these findings.

Linezolid, as contained in **ELTURIN 600,** is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not induce or inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced medicine interactions are expected. Medicines such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with **ELTURIN 600** without changes in dosage regimen.

No interactions have been observed in pharmacokinetic studies with either aztreonam or gentamicin.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the use of linezolid in pregnant women. Studies in animals have shown

reproductive toxicity. A potential risk for humans exists.

ELTURIN 600 should therefore not be used during pregnancy. **Breastfeeding**

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration.

Fertility

In animal studies, linezolid caused a reduction in fertility.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or symptoms of visual impairment (as described in section 4.8) whilst receiving **ELTURIN 600** and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8 Undesirable effects

Those most commonly reported were headache, diarrhoea, nausea, vomiting, metallic taste, abnormal liver function tests and vaginal moniliasis.

The following side effects have been reported:

Infections and Infestations:

Frequent: Moniliasis oral candidiasis, vaginal candidiasis, fungal infections.

Less frequent: Antibiotic-associated colitis, including pseudomembranous colitis.

Blood and the lymphatic system disorders:

Less frequent: Reversible anaemia, eosinophilia, leukopenia, neutropenia, thrombocytopenia, pancytopenia , myelosuppression, sideroblastic anaemia.

Immune system disorders:

Less frequent: Angioedema and anaphylaxis.

Metabolism and nutrition disorders:

Less frequent: Hyperglycaemia, lactic acidosis, Hyponatraemia.

Psychiatric disorders:

Frequent: Insomnia.

Nervous system disorders:

Frequent: Headache, taste alteration (metallic taste).

Less frequent: Dizziness, hypoaesthesia, paraesthesia, peripheral neuropathy, convulsions.

Eye disorders:

Less frequent: Blurred vision, optic neuropathy, changes in visual defect, optic neuritis, loss of vision, changes in visual acuity, changes in colour vision.

Ear and labyrinth disorders:

Less frequent: Tinnitus.

Cardiac disorders:

Less frequent: Dysrhythmia (tachycardia).

Vascular disorders:

Less frequent: Hypertension, hypotension, transient ischemic attacks, phlebitis/thrombophlebitis.

Gastro-intestinal disorders:

Frequent: Abdominal pain, cramps or distension, diarrhoea, nausea, vomiting.

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

Skin and subcutaneous tissue disorders:

Frequent: Pruritus, rash.

Less frequent: Dermatitis, diaphoresis, urticaria, angioedema, bullous skin disorders such as those described as Stevens Johnson syndrome and toxic epidermal necrolysis, alopecia.

Renal and urinary disorders:

Frequent: Increased BUN (blood urea nitrogen levels).

Less frequent: Renal failure, increased creatinine, polyuria.

Reproductive system and breast disorders:

Less frequent: Vulvovaginal disorder, vaginitis.

General disorders and administrative site conditions:

Less frequent: Chills, fatigue, fever, localised pain.

Investigations: Chemistry

Frequent: Increased total bilirubin, AST, ALT, LOH, alkaline phosphatase, BUN, 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.

Investigations: Haematology

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

Less frequent: Increased reticulocyte count; decreased neutrophils.

4.9 Overdose

Symptoms:

No cases of overdose have been reported. In the event of an overdose, an exacerbation of side effect could be expected.

Treatment:

Supportive care is advised together with maintenance of glomerular filtration. Approximately 30 % of an **ELTURIN 600** dose is removed during 3 hours of haemodialysis, but no data are available for the removal of **ELTURIN 600** by peritoneal dialysis or haemoperfusion. The two primary metabolites of **ELTURIN 600** are also removed to some extent by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmaceutical groups:

Category and class: A20.1.1 Broad and medium spectrum antibiotic.

ATC code: J01XX08

Linezolid is a synthetic antibacterial medicine of the oxazolidinone class of antibiotics. It has *in vitro* activity against aerobic Gram-positive bacteria and anaerobic microorganisms. It selectively inhibits bacterial protein synthesis through binding to sites on the bacterial ribosome and prevents the formation of a functional 70S-initiation complex that is an essential component of the translation process.

Resistance: Linezolid's mechanism of action differs from that of other antibiotics (e.g. the aminoglycosides, beta lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol). Therefore, there is no cross-resistance between linezolid and these classes of medicines.

In vitro studies have shown that 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}.

Resistance to linezolid has been reported in enterococci. *Staphylococcus aureus* and coagulase negative staphylococci.

5.2 Pharmacokinetic properties

ELTURIN 600 contains linezolid that is biologically active and is metabolised to form inactive metabolites. The aqueous solubility of linezolid is approximately 3 mg/mL and is independent of pH between pH 3 to 9.

Absorption:

Maximum plasma concentrations are reached within 2 hours of dosing and absolute bioavailability is approximately 100 %. It is not affected by food.

Distribution:

The volume of distribution at steady-state averages at about 40 to 50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31 %.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in volunteer studies following multiple dosing. The ratio of linezolid in saliva and sweat relative to plasma was 1,2:1,0 and 0,55:1,0 respectively.

The ratio for epithelial lining fluid and alveolar cells of the lung was 4,5:1,0 and 0,15:1,0, when measured at steady-state C_{max} respectively. In a small study of subjects with ventricular-peritoneal shunts and essentially non-inflamed meninges, the ratio of linezolid in cerebrospinal fluid to plasma at C_{max} was 0,7:1,0 after linezolid dosing.

Biotransformation:

Linezolid is metabolised by a non-enzymatic process. Metabolic oxidation of the morpholine ring results primarily in 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 detectably 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:

Under steady-state conditions, linezolid is primarily excreted in the urine as metabolite B (40 %), parent drug (30 - 35 %) and metabolite A (10 %). The elimination half-life of the parent drug averages at about 5 -7 hours. Non-renal clearance accounts for approximately 65 % of the total clearance of linezolid.

Special populations:

Elderly:

The pharmacokinetics of linezolid is not significantly altered in elderly patients aged 65 and over.

Renal insufficiency:

No dose adjustment is necessary in patients with either mild, moderate or severe renal insufficiency, as linezolid clearance is independent of creatinine clearance. There is evidence that the primary metabolites of linezolid accumulate in patient with severe renal insufficiency (i.e. CL_{CR}< 30 mL/min).

The clinical significance of this has not yet been established. As approximately 30 % of a dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration). Linezolid should be given after dialysis in patients receiving such treatment.

Hepatic insufficiency:

The pharmacokinetics of linezolid is not altered in patients with mild to moderate hepatic insufficiency. Dose adjustment in such patients is, therefore, not required. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency has not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Children:

The pharmacokinetics of linezolid following a single IV dose was investigated in paediatric patients ranging in age from birth through 17 years (including premature and full-term neonates).

The C_{max} and the volume of distribution (V_{ss}) are similar regardless of age in paediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from > 1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of paediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values approach these observed for the adult population. There is wider inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all paediatric age groups as compared with adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ELTURIN 600 contains colloidal anhydrous silica, crospovidone, hydrogenated polyoxyl castor oil, magnesium stearate, microcrystalline cellulose, povidone (K 30) and sodium starch glycolate. The film coating contains hypromellose, macrogol 6000, purified talc and titanium dioxide.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months from the manufacturing date.

6.4 Special precautions for storage

Store at or below 30 °C. Keep the strip in the carton until required for use.

Store in the original package in order to protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Tablets are packed in a blister pack of hard tempered aluminium foil and PVC film or in a strip pack of Aluminium /Aluminium foil laminated with low–density polyethylene film and further packed in an outer carton in packs of 10, 20, 30 or 100 tablets.

Not all packs and pack sizes are necessarily marketed.

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

No special requirements.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

MACLEODS PHARMACEUTICALS SA (PTY) LTD

Ground floor, Block 1, Bassonia Estate Office Park (East),

1 Cussonia Drive, Bassonia Rock, Ext. 12, Alberton.

8. REGISTRATION NUMBER(S)

54/20.1.1/0235

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 May 2020

10. DATE OF REVISION OF THE TEXT

07 August 2023

PM0103-01