WHO-PQ RECOMMENDED SUMMARY OF PRODUCT CHARACTERISTICS

This summary of product characteristics focuses on uses of the medicine covered by WHO's Prequalification Team - Medicines. The recommendations for use are based on WHO guidelines and on information from stringent regulatory authorities.[*]

The medicine may be authorised for additional or different uses by national medicines regulatory authorities.

[*]https://extranet.who.int/pqweb/sites/default/files/documents/75%20SRA%20clarification_Feb2017_newtempl.pdf

1. NAME OF THE MEDICINAL PRODUCT

[TB389 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each dispersible tablet contains Linezolid 150 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

White to off-white, circular flat-faced, beveled edge, uncoated tablets with deep break-line on one face and shallow convex debossed with “LD” on other face.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB389 trade name] is indicated in combination with other tuberculosis medicines for the treatment of drug-resistant tuberculosis caused by *Mycobacterium tuberculosis*.

Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

4.2 Posology and method of administration

Treatment with [TB389 trade name] should be initiated and monitored by a physician experienced in the management of multidrug-resistant *Mycobacterium tuberculosis*.

[TB389 trade name] should always be used in combination with other tuberculosis medicines. Consideration should be given to WHO guidelines when selecting the appropriate combination regimen.

Posology

[TB389 trade name] is for use in children weighing from 3 to 46 kg receiving longer individualised regimens for multidrug-resistant TB.

The following dose recommendations for children are based on a dose of 15 mg/kg once daily in children weighing 3–14 kg or 10–12 mg/kg once daily in children weighing 15 kg or more:

Child’s weight	**Number of 150-mg dispersible tablets**	**Dose in mg**
3 to less than 5 kg	See under Method of administration, below	37.5 mg daily
5 to less than 7 kg	See under Method of administration, below	75 mg daily
7 to less than 16 kg	1 tablet daily	150 mg daily
16 to less than 24 kg	2 tablets daily	300 mg* daily
24 to less than 36 kg	2 tablets daily	300 mg daily
36 to less than 46 kg	3 tablets daily	450 mg daily
46 kg and over	*As for adults***	
* in children weighing 16 to less than 24 kg, the dose will exceed 10–12 mg/kg, and a dose of 225 mg (1½ tablets) may be given as 15 mL of a solution prepared by dispersing two 150-mg tablets in 20 mL of water		

† Trade names are not prequalified by WHO. This is the national medicines regulatory agency’s responsibility.

**	Alternative formulations supplying higher amounts of active substance are preferrable.

[TB389 trade name] is not recommended in children weighing less than 3 kg.

Treatment duration

The duration of tuberculosis treatment depends on the regimen chosen, the patient's clinical and radiographical responses, smear and culture results, and susceptibility of *Mycobacterium tuberculosis* isolates from the patient or the suspected source case.

Typically, a total treatment duration of 18–20 months and a treatment duration of 15–17 months after culture conversion are suggested for most patients, with the duration being modified according to the patient's response to therapy.

Special populations

Renal impairment

No dose adjustment is required, including in patients with severe renal impairment (creatinine clearance less than 30 mL/minute) (see sections 4.4 and 5.2). However, linezolid 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, because the clinical significance of higher exposure (up to 10 fold) to the two primary metabolites of linezolid is unknown.

As 3-hour haemodialysis removes about 30% of a linezolid dose, linezolid should be given after dialysis. Haemodialysis removes the primary metabolites of linezolid to some extent, but the concentrations of these metabolites are still very considerably higher after dialysis than those in patients with normal renal function or mild to moderate renal insufficiency. Linezolid should, therefore, be used with special caution in patients on dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

There is no experience of linezolid administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than haemodialysis).

Hepatic impairment

Limited clinical data are available in patients with hepatic impairment. Linezolid should, therefore, be given with caution to patients with liver dysfunction and only when the anticipated benefit is considered to outweigh the theoretical risk (see sections 4.4 and 5.2).

Method of administration

Oral administration.

[TB389 trade name] may be taken with food or between meals.

Children weighing 7 kg or more

The required number of [TB389 trade name] tablets (see table above) should be dispersed in a small amount of water (about 10 mL per tablet) and thoroughly mixed. The entire mixture (water and tablets) should be swallowed immediately. The cup or glass that contained the mixture should then be rinsed with a small amount of water and the contents swallowed to ensure the entire dose is taken.

If it is necessary to use a volume less than 10 mL for dispersing a tablet, or to give a portion of the dispersed mixture to supply the correct dose, then a suitable oral syringe should be provided to measure the required volume and careful instructions given on how to disperse the tablet and measure the correct dose.

Children less than 7 kg

For children weighing less than 7 kg, one tablet should be dispersed in 10 mL water and thoroughly mixed. The child should be given a proportion of the mixture as follows:

Child's weight	Volume to be given after dispersing 1 tablet in 10 mL water	Dose in mg
3 to less than 5 kg	2.5 mL daily†	37.5 mg daily
5 to less than 7 kg	5 mL daily†	75 mg daily
† An oral syringe should be provided to measure volumes less than 10 mL		

Missed dose

If the patient misses a dose of [TB389 trade name] within 12 hours of the usual scheduled time, the patient should take the dose as soon as possible and take the next dose at the usual scheduled time. If the patient misses a dose by more than 12 hours, the patient should not take the missed dose and instead take the next dose at the usual scheduled time. The patient should not double the dose to make up for a missed dose.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Linezolid must not be used in patients taking any medicine which inhibits monoamine oxidases A or B (e.g. isocarboxazid, moclobemide, phenelzine, selegiline) or within 2 weeks of taking any such medicine.

Unless blood pressure can be closely monitored, linezolid must not be administered to:

- patients with uncontrolled hypertension, phaeochromocytoma, carcinoid syndrome, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states
- patients taking serotonin re-uptake inhibitors (see section 4.4), tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), directly and indirectly 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.

4.4 Special warnings and precautions for use

Potentially serious adverse effects – particularly anaemia, thrombocytopenia, lactic acidosis, peripheral neuropathy and optic neuropathy – may occur with linezolid, and the risk increases with duration of treatment. **Close monitoring** is strongly advised **throughout treatment.**

Myelosuppression

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. This can be severe and life threatening. These effects were on some occasions reversed by lowering the dose (usually from 600 mg daily to 300 mg daily). Haematological toxicity is more frequent and severe after more than 28 days of treatment but is less common with current strategies of once-daily dosing.

Elderly patients treated with linezolid may be at greater risk of blood dyscrasias than younger patients. Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis.

Complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) are recommended **weekly** in patients who receive linezolid, regardless of baseline blood count. This is even more important in patients who:

- have 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.

Linezolid 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 therapy, treatment should be stopped unless continuing therapy is absolutely necessary, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pre-treatment levels.

Cases of sideroblastic anaemia have been reported. Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered after discontinuation of linezolid with or without treatment for their anaemia.

Lactic acidosis

Lactic acidosis has been reported with the use of linezolid. Patients should receive immediate medical attention if they develop signs and symptoms of metabolic acidosis including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level, or hyperventilation while receiving linezolid. If lactic acidosis occurs, the benefits of continuing linezolid should be weighed against the potential risks.

Antibiotic-associated diarrhoea and colitis

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridioides difficile* (*Clostridium difficile*)-associated diarrhoea, has been reported in association with the use of 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, treatment with antibacterial agents, including linezolid, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs inhibiting peristalsis are contraindicated in this situation.

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 the drug is used longer than 28 days.

Serotonin syndrome

There have been reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) (see section 4.5). Therefore, linezolid should not usually be co-administered with serotonergic agents, such as serotonin re-uptake inhibitors, tricyclic antidepressants and serotonin 5-HT_1 receptor agonists (triptans), except where both are essential. In those cases patients should be closely observed for signs and symptoms of serotonin syndrome which may include early tremor, clonus and hyperreflexia, incoordination, confusion, frank delirium, labile blood pressure and hyperpyrexia. If signs or symptoms occur, health care providers should consider discontinuing either one or both agents; if the serotonergic agent is stopped, withdrawal symptoms can occur.

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; the risk increases with duration of treatment. Peripheral neuropathy may or may not improve on stopping linezolid. The outcome of optic neuropathy after stopping linezolid is less clear, and it should be treated as a medical emergency.

If possible, patients' visual function should be regularly monitored. Ophthalmological examination should include tests for black-white/chromatic visual acuity (e.g. Snellen eye chart and 65-test) and ophthalmoscopy; tests should be repeated if any change in acuity or colour vision is suspected. All patients should be advised to report any 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 peripheral or optic neuropathy occurs, the continued use of linezolid should be weighed against the potential risks.

Convulsions

Convulsions have been reported in patients when treated with linezolid. In most cases, a history of seizures or risk factors for seizures was reported. Patients should be advised to inform their health care providers if they have a history of seizures.

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI) and use with other MAOIs or in circumstances where MAO inhibition may be a risk should normally be avoided (see section 4.5).

Use with tyramine-rich foods

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

Superinfection

The effects of linezolid on normal flora have not been evaluated in clinical trials.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. Appropriate measures should be taken if superinfection occurs during therapy.

Special populations

Linezolid 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 (see sections 4.2 and 5.2).

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk (see sections 4.2 and 5.2).

Impairment of fertility

For the need to consider the potential risk of reduced male fertility when treating adolescents and post-pubertal boys see section 4.6.

Potential interactions producing elevation of blood pressure

Linezolid can enhance increases in blood pressure caused by drugs with a vasopressor action (see section 4.5). Linezolid and drugs with vasopressive action should, therefore, not be co-administered, except when concomitant use of these drugs is essential.

4.5 Interaction with other medicinal products and other forms of interaction

Potential interactions producing elevation of blood pressure

In normotensive volunteers, co-administration of linezolid with either pseudoephedrine or phenylpropanolamine resulted in mean increases in systolic blood pressure of about 30–40 mm Hg, compared with 11–15 mm Hg increases with linezolid alone, 14–18 mm Hg with either pseudoephedrine or phenylpropanolamine alone and 8–11 mm Hg with placebo. Studies in hypertensive individuals have not been conducted. Concomitant use of linezolid and pseudoephedrine or phenylpropanolamine is, therefore, contraindicated (see section 4.3).

Linezolid should not be co-administered with other agents with a vasopressor action, unless concomitant use is essential. It is recommended that doses of directly and indirectly acting sympathomimetic agents (including adrenergic bronchodilators), vasopressors (e.g. epinephrine [adrenaline], norepinephrine [noradrenaline]), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone, should be carefully titrated to achieve the desired response when co-administered with linezolid.

Potential serotonergic interactions

The potential interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20 mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

Post marketing experience: there has been one report of a patient experiencing serotonin syndrome- like effects while taking linezolid and dextromethorphan which resolved on discontinuation of both medications.

During clinical use of linezolid with ***serotonergic agents***, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), cases of serotonin syndrome have been reported. Therefore, although linezolid and serotonergic agents, such as SSRIs, tricyclic antidepressants, or serotonin 5-HT_1 receptor agonists (triptans), should not usually be co-administered (section 4.3), management of patients for whom treatment with linezolid and serotonergic agents is essential is described in section 4.4.

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAO) but at the doses used for antibacterial therapy, it does not have an antidepressant effect. There are very limited data from drug interaction studies on the safety of linezolid when administered to patients on concomitant medications that might put them at risk from excessive MAO inhibition. Therefore, linezolid must not be used with certain medicines (e.g. isocarboxazid, moclobemide, phenelzine, selegiline, see also section 4.3) and should not be used with other medicines where MAO inhibition may be a risk unless close observation and blood pressure monitoring of the recipient is possible.

Drugs metabolised by cytochrome P450

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced drug interactions are expected with linezolid.

Rifampicin

The effect of rifampicin on the pharmacokinetics of linezolid was studied in 16 healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the mean linezolid C_{max} by 21% [90% CI, 15, 27] and the mean linezolid AUC by 32% [90% CI, 27, 37]. The mechanism of this interaction and its clinical significance are unknown.

Warfarin

When warfarin was added to linezolid 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 linezolid to assess the clinical significance of these findings.

Zidovudine

In patients co-infected with tuberculosis and HIV, concomitant use of linezolid-based therapy and an antiretroviral regimen including zidovudine requires special caution, since both zidovudine and linezolid may cause peripheral nerve toxicity and myelosuppression.

Use with tyramine-rich foods

No significant pressor response was observed in individuals receiving both linezolid and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting excessive 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).

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are limited data on the use of linezolid in pregnant women but no reports of increased malformation or other direct or indirect harmful effects on the human fetus. The adverse effects of linezolid may be exacerbated by the physiological effects of pregnancy, which lead to a relatively low haemoglobin (due to the dilutional effect of increased blood volume) and a higher risk of peripheral neuropathies at treatment baseline compared with non-pregnant patients. Studies in animals have shown reproductive toxicity (see section 5.3).

Linezolid should be used during pregnancy only if clearly necessary, i.e. only if the potential benefit outweighs the possible risk.

Breast-feeding

Linezolid is present in human milk. Limited data indicate that the maximum dose an infant would receive through breastmilk would be only 6 to 9% of the standard infant dose. There is no information on the effects of linezolid on the breast-fed infant; however, diarrhoea and vomiting were the most common adverse reactions reported in clinical trials in infants receiving linezolid therapeutically.

Given the benefit of tuberculosis therapy in the mother, a decision must be made whether to discontinue breast-feeding taking into account the benefit of breast feeding for the child.

Fertility

In animal studies, linezolid reduced male fertility (see section 5.3). These effects were reversible in adult animals, but did not reverse in juvenile animals treated with linezolid for nearly the entire period of sexual maturation. There were no adverse effects on female fertility.

The effect on fertility in humans is unknown. The potential risk of reduced male fertility should be taken into account when treating adolescents and post-pubertal boys.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or symptoms of visual impairment (see sections 4.4 and 4.8) while taking linezolid and should be advised not to drive or operate machines if any of these symptoms occur.

4.8 Undesirable effects

Most of the data on the adverse effects of linezolid does not come from patients with tuberculosis but from patients with other conditions using higher doses of linezolid for less than 4 weeks.

Adverse events

The most commonly reported adverse reactions are diarrhoea, headache, nausea and vomiting. About 3% of patients on short-term linezolid discontinued treatment because of a drug-related adverse event. Around 30% of patients prescribed linezolid as part of longer (18-month) regimens for drug-resistant tuberculosis discontinue linezolid within 6 months.

The adverse reactions listed below uses the following convention for frequency: very common (more than 1 in 10); common (1/100 to 1/10); uncommon (1/1000 to 1/100); rare (1/10 000 to 1/1000); very rare (less than 1/10 000); and not known (cannot be estimated from the available data).

Infections and infestations

Common	candidiasis including oral and vaginal candidiasis; fungal infections
Uncommon	vaginitis

Blood and lymphatic disorders

Common	anaemia*†
Uncommon	leucopenia*; neutropenia; thrombocytopenia*; eosinophilia
Rare	pancytopenia*
Not known	myelosuppression; sideroblastic anaemia*

Immune system disorders

Not known	anaphylaxis

Metabolic and nutrition disorders

Uncommon	hyponatraemia
Not known	lactic acidosis*

Psychiatric disorders

Common	insomnia

Nervous system disorders

Common	headache; taste perversion (metallic taste); dizziness
Uncommon	convulsions*; hypoaesthesia; paraesthesia
Not known	serotonin syndrome**; peripheral neuropathy*

Eye disorders

Uncommon	blurred vision*
Rare	changes in visual field (defect)*
Not known	optic neuropathy*; optic neuritis*; loss of vision*; changes in visual acuity*; changes in colour vision*

Ear and labyrinth disorders

Uncommon	tinnitus

Cardiac disorders

Uncommon	arrhythmia (tachycardia)

Vascular disorders

Common	hypertension†
Rare	transient ischaemic attacks†

Gastrointestinal disorders

Common	diarrhoea, nausea, vomiting, localised or general abdominal pain†, constipation, dyspepsia
Uncommon	pancreatitis; gastritis; abdominal distention; dry mouth; glossitis; loose stools; stomatitis; tongue discoloration or disorder
Rare	superficial tooth discoloration; antibiotic-associated colitis, including pseudomembranous colitis*

Hepatobiliary disorders

Common	abnormal liver function test; increased AST, ALT or alkaline phosphatase
Uncommon	increased total bilirubin

Skin and subcutaneous tissue disorders

Common	pruritus, rash
Uncommon	urticaria; dermatitis; diaphoresis
Not known	bullous disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis; angioedema; alopecia

Renal and urinary disorders

Common	increased BUN
Uncommon	renal failure; increased creatinine; polyuria

Reproductive system and breast disorders

Uncommon	vulvovaginal disorder

General disorders and administration site conditions

Common	fever
Uncommon	chills; fatigue; increased thirst

Investigations

Common	Chemistry increased LDH, creatine kinase, lipase, amylase or non-fasting glucose; decreased total protein, albumin, sodium or 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.
Uncommon	Chemistry increased calcium; decreased non fasting glucose; increased or decreased sodium or chloride. Haematology increased reticulocyte count; decreased neutrophils.

* See section 4.4

** See sections 4.3 and 4.4

†The following adverse reactions to linezolid were considered to be serious in rare cases: localised abdominal pain, transient ischaemic attacks and hypertension.

In controlled clinical trials where linezolid was administered for up to 28 days, 2.0% of the patients reported anaemia. In a compassionate use programme of patients with life-threatening infections and underlying co-morbidities, the patients who developed anaemia when receiving linezolid for less than 28 days was 2.5% (33/1326) compared with 12.3% (53/430) when treated for more than 28 days. The proportion of cases with drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for less than 28 days and 15% (8/53) in those treated for more than 28 days.

A meta-analysis of longer-term tuberculosis regimens included experience from over 300 patients treated with linezolid for at least 1 month, mostly at a dose of 600 mg/day. About 30% received linezolid for only 1–6 months but over 30% received it for more than 18 months. No clear pattern could be discerned for type of adverse event and duration of use; a few cases of optic neuropathy were reported, which is known to be associated with long-term use of linezolid, but haematological toxicity was reported regardless of duration of use.

A study involving 108 patients with extensively drug-resistant or multidrug-resistant tuberculosis given the regimen comprising bedaquiline, pretomanid and linezolid for 6 to 9 months, in which dosage reduction of linezolid after the first month was permitted to manage adverse events, found that overall, 18 patients (17.3%) completed a full course of linezolid at the recommended dose of 1200 mg daily, 38 (36.5%) completed with a 600-mg dose, 16 (15.4%) completed with a 300-mg dose and 32 (30.7%) stopped linezolid early due to an adverse event.

Paediatric population

Safety data from clinical studies based on more than 500 paediatric patients (from birth to 17 years) do not indicate that the safety profile of linezolid for paediatric patients differs from that for adult patients.

Reporting of suspected adverse reactions

Health care providers are asked to report adverse reactions that may be linked to a medicine, to the marketing authorisation holder, or, if available, to the national reporting system. Reports of suspected adverse reactions to a medicine are important for the monitoring of the medicine's benefits and risks.

4.9 Overdose

Symptoms

No cases of overdose have been reported. Signs of toxicity in rats after doses of 3000 mg/kg/day linezolid were decreased activity and ataxia whilst dogs treated with 2000 mg/kg/day experienced vomiting and tremors.

Treatment

No specific antidote is known.

General supportive and symptomatic care is advised together with maintenance of glomerular filtration. About 30% of a linezolid dose is removed during 3 hours of haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antibacterials, ATC code: J01XX08.

Mechanism of action

Linezolid is a synthetic, antibacterial agent that belongs to the class of oxazolidinones. It has activity against aerobic Gram-positive bacteria and anaerobic micro-organisms in vitro. Linezolid selectively inhibits bacterial protein synthesis by binding to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

The wild-type linezolid minimum inhibitory concentration (MIC) distribution for clinical isolates of *Mycobacterium tuberculosis* has been reported to range from 0.125 to 0.5 mg/mL, with a suggested epidemiological wild-type cut-off (ECOFF) of 0.5 mg/mL.

PK/PD relationship

In animal studies, the key pharmacodynamic parameter for efficacy was the time for which the linezolid plasma level exceeded the MIC for the infecting organism. Target values of AUC/MIC ratio > 100 and time above MIC > 85% for linezolid in the treatment of infections caused by Gram-positive microorganisms in humans have been reported.

The target values of these PK/PD indices for *M. tuberculosis* infection have not been established.

Mechanisms of resistance

Resistance to linezolid, defined as MIC ≥ 1 µg/mL, ranging from 1.9% to 5.9% in clinical MDR *M. tuberculosis* isolates has been reported in several studies of over 500 clinical isolates from different geographic locations.

Although the exact mechanisms of resistance are not completely known, resistance was related to mutations in the 23S rRNA and mutation T460C in *rplC*, encoding the 50S ribosomal L3 protein. In addition, data suggest a non-ribosomal mechanism of resistance and possible involvement of efflux pumps.

Clinical experience

Limited data are available on the efficacy and safety of linezolid in the treatment of MDR-TB.

In a randomised controlled trial in 65 patients with sputum-culture-positive extensively drug-resistant tuberculosis, patients received a 2-year, individualised regimen with or without linezolid (starting dose of 1200 mg/day for 4–6 weeks followed by a dose of 300–600 mg/day). Treatment duration ranged from 6 to 24 months with an average of about12 months. By 24 months, 78.8% of patients in the linezolid group and 37.6% of patients in the control group had negative cultures ($p < 0.001$). Treatment success rates were 69.7% (23/33) in the linezolid group and 34.4% (11/32) in the control group ($p = 0.004$).

Another randomised controlled trial enrolled 41 patients with sputum-culture-positive extensively drug-resistant tuberculosis whose infection did not respond to any available medicines during the previous 6 months. Patients received linezolid (600 mg/day), immediately or after 2 months in addition to their background regimen. After confirmed sputum-smear conversion or 4 months, patients were randomised to continued 600 mg/day or 300 mg/day linezolid for at least an additional 18 months. By 4 months, 79% (15/19) of the patients in the immediate-start group and 35% (7/20) in the delayed-start group had culture conversion ($p = 0.001$). One year after end of treatment, 71% (27/38) of patients who received linezolid had negative sputum cultures.

A systematic review reported a pooled sputum culture conversion rate of 88.45% (95% CI = 83.82–92.38%) based on 507 patients from 23, mostly observational, studies. Linezolid doses were 300 to 1200 mg/day and treatment duration ranged from 1 to 36 months.

A Phase 3 partially blinded, randomised trial assessed the safety and efficacy of various doses and treatment durations of linezolid plus bedaquiline and pretomanid in patients with pulmonary multidrug-resistant or extensively drug-resistant tuberculosis. Participants received 26 weeks of treatment with linezolid plus bedaquiline and pretomanid. Each of the four arms varied the dose and duration of linezolid: 1200 mg for 26 weeks, 1200 mg for 9 weeks, 600 mg for 26 weeks or 600 mg for 9 weeks. Participants with MDR/RR-TB (with or without fluoroquinolone resistance) receiving linezolid 600 mg for 26 weeks (n = 43) had higher levels of treatment success (100% vs 98%), lower levels of failure and recurrence (0% vs 2.3%) and fewer Grade 3–5 adverse events (14% vs 18.6%) than those given 1200 mg for 26 weeks.

Further analysis comparing the 33 patients in this trial receiving linezolid 600 mg daily for 26 weeks with participants receiving longer regimens for MDR/RR-TB (n = 839) showed that that the former had higher levels of treatment success (100% vs 75%) and lower levels of failure and recurrence (0% vs 6.6%).

5.2 Pharmacokinetic properties

The absorption characteristics of [TB389 trade name] have been determined after administration of four (4) tablets of [TB389 trade name] in healthy volunteers in the fasting state as follows:

Pharmacokinetic variable	**Mean value* (± standard deviation)**
Maximum concentration (C_{max})	16.7 ± 3.8 µg/mL
Area under the curve ($AUC_{0-\infty}$), a measure of the extent of absorption	136 ± 29 µg.h/mL
Time to attain maximum concentration (T_{max})	1.17 ± 0.85 hours

Pharmacokinetics of linezolid

	Linezolid
Absorption	
Absolute bioavailability	Approximately 100%
Oral bioavailability	Approximately 100%.

	Steady-state conditions are achieved by the second day of dosing.
Food effect	Oral absorption is not significantly affected by food intake.
Distribution	
Volume of distribution (mean)	40–50 L
Plasma proteinbinding *in vitro*	31% and not concentration dependent
Tissue distribution	Sweat/plasma: 1.2 Saliva/plasma: 0.55 Ratios at $C_{max\ ss}$: Epithelial lining fluid/plasma: 4.5 Alveolar cells/plasma: 0.15 CSF/plasma: 0.7 (non-inflamed meninges)
Metabolism	
	Primarily metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives; the predominant hydroxyethyl glycine metabolite (PNU-142586), believed to be formed by a non-enzymatic process and the less abundant aminoethoxyacetic acid metabolite (PNU-142300).
Elimination	
Elimination half life	about 5–7 h
Mean systemic clearance (Cl/F)	After single dose 7.62 L/h After multiple dose: 4.8 L/h
% of dose excreted in urine	Under steady-state conditions primarily excreted as PNU-142586 (40%), parent drug (30%) and PNU-142300 (10%)
% of dose excreted in faeces	Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. Virtually no parent drug is found in the faeces, approximately 6% and 3% of each dose appears as PNU-142586 and PNU-142300, respectively.
Pharmacokinetic linearity	A small degree of non-linearity in clearance is observed with increasing doses of linezolid. This appears to be due to lower renal and non-renal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.
Drug interactions *(in vitro*)	Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes.

Special populations

Renal impairment

Pharmacokinetics are not altered by mild to moderate renal impairment. After single doses of 600 mg, there was a 7–8 fold increase of the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e. creatinine clearance < 30 mL/minute). However, the AUC of the parent drug did not increase. Although there is some removal of the major metabolites of linezolid by haemodialysis, metabolite plasma levels after single 600-mg doses were still considerably higher after dialysis than those in patients with normal renal function or mild to moderate renal insufficiency.

In 24 patients with severe renal insufficiency, 21 of whom were on regular haemodialysis, peak plasma concentrations of the two major metabolites after several days dosing were about 10 fold those of patients with normal renal function. Peak plasma levels of linezolid were not affected.

The clinical significance of these observations has not been established as limited safety data are currently available.

Hepatic impairment

Limited data indicate that the pharmacokinetics of linezolid, PNU-142300 and PNU-142586 are not altered in patients with mild to moderate hepatic insufficiency (i.e. Child-Pugh class A or B). The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e. Child-Pugh class C) have not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function is not expected to significantly alter its metabolism.

Paediatric population (< 18 years old)

There are limited data on the safety and efficacy of linezolid in children and adolescents (< 18 years old). Pharmacokinetic studies indicate that after single and multiple doses in children (1 week to 12 years), linezolid clearance (based on kg body weight) was greater in paediatric patients than in adults, but decreased with increasing age.

In children 1 week to 12 years old, administration of 10 mg/kg every 8 hours daily gave exposure approximating to that achieved with 600 mg twice daily in adults.

In adolescents (12 to 17 years old), linezolid pharmacokinetics were similar to that in adults following a 600-mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that in adults receiving the same dosage.

In paediatric patients with ventriculoperitoneal shunts who were administered linezolid 10 mg/kg either 12 hourly or 8 hourly, linezolid concentrations in the cerebrospinal fluid (CSF)were variable after either single or multiple dosing of linezolid. Therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, linezolid is not recommended for the empirical treatment of paediatric patients with central nervous system infections.

Elderly

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

Female patients

Females have a slightly lower volume of distribution than males and the mean clearance is reduced by about 20% when corrected for body weight. Plasma concentrations are higher in females and this can partly be attributed to body weight differences. However, because the mean half-life of linezolid is not significantly different in males and females, plasma concentrations in females are not expected to rise substantially above those known to be well tolerated; therefore, dose adjustments are not required.

5.3 Preclinical safety data

General toxicity

Preclinical data, based on conventional studies of repeated-dose toxicity and genotoxicity, revealed no special hazard beyond those mentioned below. Carcinogenicity / oncogenicity studies have not been conducted.

Linezolid produced reversible myelosuppression in rats and dogs. In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in one male at this dose level at a 3-month interim necropsy. Minimal to moderate optic nerve degeneration was evident in 2 of 3 male rats after 6 months of dosing, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The optic nerve degeneration observed was microscopically comparable to spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of common background change.

Reproductive toxicity

A reversible decrease in fertility was observed in male rats exposed to linezolid as adults. Non-viable spermatids, epithelial cell hypertrophy, and hyperplasia in the epididymis occurred at dose levels comparable to or greater than human exposure levels. In sexually mature animals these effects were reversible. However, these effects did not reverse in juvenile animals treated with linezolid for nearly the entire period of sexual maturation. Abnormal sperm morphology in testis of adult male rats, and epithelial cell hypertrophy and

hyperplasia in the epididymis were noted. Linezolid appeared to affect the maturation of rat spermatozoa. There were no adverse effects on female fertility.

Linezolid did not cause congenital malformations in mice and rats at dose levels causing maternal toxicity, decreased embryo viability, and decreased fetal weight. At these maternally toxic dose levels, there was an increase in resorptions and post-implantation fetal loss and a decrease in fetal weight in the mice. In the rat study, there was a decrease in fetal weight. Fetal skeletal abnormalities occurred that were consistent with general fetal toxicity.

Linezolid and its metabolites are present in the milk of lactating rats and the concentrations were higher than those in maternal plasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: Microcrystalline cellulose
Ethylcellulose
Sucralose
Peppermint flavour
Orange flavour
Crospovidone
Croscarmellose sodium
Colloidal anhydrous silica
Magnesium stearate

This medicine is essentially ‘sodium-free’. It contains less than 1 mmol sodium (23 mg) per tablet.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

48 months

6.4 Special precautions for storage

Do not store above 30°C. Avoid excursions above 30°C.

6.5 Nature and contents of container

Strip pack
The tablets are packed in ALU/ALU strip pack. Each pack contains 10x10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

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

7. SUPPLIER

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References

WHO consolidated guidelines on tuberculosis, Module 4: Treatment. Drug-resistant tuberculosis treatment 2022. Available at: https://tbksp.org/node/5

WHO operational handbook on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment (2020), Available at: https://tbksp.org/node/2226

WHO consolidated guidelines on tuberculosis, Module 5: Management of tuberculosis in children and adolescents: 2022 Available at: https://tbksp.org/node/1731

WHO operational handbook on tuberculosis: module 5: Management of tuberculosis in children and adolescents (2022). Available at: https://tbksp.org/node/1730

UK SmPC for Zyvox (updated 17 Sep 2018). Available at: https://www.medicines.org.uk/emc/product/1688/smpc

Further references relevant to sections of the SmPC include:

Section 4.6

Drugs During Pregnancy and Lactation Treatment Options and Risk Assessment Third Edition 2015 Elsevier

Drugs and Lactation Database (LactMed) Bethesda (MD): National Library of Medicine (US); 2006-.

Section 5.1

Schön T, Juréen P, Chryssanthou E, Giske CG, Sturegård E, Kahlmeter G, Hoffner S, Ängeby KA. Wild-type distributions of seven oral second-line drugs against *Mycobacterium tuberculosis*. The International Journal of Tuberculosis and Lung Disease 2011;15(4):502-509.

Rayner CR, Forrest A, Meagher AK, Birmingham MC and Schentag JJ. Clinical pharmacodynamics of linezolid in seriously ill patients treated in a compassionate use programme. Clin. Pharmacokinet. 2003;42**:**1411-1423.

Maartens G, Benson CA. Linezolid for Treating Tuberculosis: A Delicate Balancing Act. EbioMedicine 2015;2(11):1568-1569.

Ahmed I, Jabeen K, Inayat R, Hasan R. Susceptibility Testing of Extensively Drug-Resistant and Pre-Extensively Drug-Resistant *Mycobacterium tuberculosis* against Levofloxacin, Linezolid, and Amoxicillin-Clavulanate.Antimicrobial Agents and Chemotherapy. 2013;57(6):2522-2525.

Richter E, Rüsch-Gerdes S and Hillemann D. First linezolid-resistant clinical isolates of *Mycobacterium tuberculosis*. Antimicrob. Agents Chemother. 2007;51:1534-1536.

Huang TS, Liu YC, Sy CL, Chen YS, Tu HZ, Chen BC. In vitro activities of linezolid against clinical isolates of *Mycobacterium tuberculosis* complex isolated in Taiwan over 10 years. Antimicrob. Agents Chemother. 2008;52:2226–2227.

Hillemann D, Rüsch-Gerdes S and Richter E. In Vitro-selected linezolid-resistant *Mycobacterium turberculosis* mutants. Antimicrob. Agents Chemother. 2008;52(2):800-801.

Tang S, Yao L, Hao X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Respir J 2015;45:161-70.

Agyeman A and Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob (2016) 15:41.

Lee M, Lee J, Carroll MW et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis N. Engl. J. Med. 2012;367(16):1508–1518.

Lee M, Cho SN, et al. Linezolid for XDR-TB — Final Study Outcomes N. Engl. J. Med. 2016;373(3):290-291.

Conradie F, Diacon AH, Ngubane N, Howell P, Everitt D, Crook AM et al. Treatment of highly drug-resistant pulmonary tuberculosis. N Engl J Med. 2020;382(10):893–902.

Detailed information on this medicine is available on the World Health Organization (WHO) website: https://extranet.who.int/pqweb/medicines