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

[TB323 trade name]†

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg linezolid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White, capsule-shaped, biconvex, film-coated tablets, with a break line on one surface and plain on the other surface.

The tablets can be divided into equal doses.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

[TB323 trade name] is indicated in combination with other antituberculosis agents 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

Posology

Adults and adolescents aged 14 years and older and weighing at least 45 kg

When used in longer regimens (typically lasting 18 to 20 months) for the treatment of multidrug-resistant tuberculosis (MDR-TB) the recommended dose of [TB323 trade name] is one 600-mg tablet daily.

The dose may be reduced to 300 mg/day or stopped altogether if serious adverse effects develop (see sections 4.4 and 4.8).

When linezolid is used in combination with bedaquiline and pretomanid (BPaL regimen) the recommended dose is 1200 mg (two tablets) daily. The dose can be reduced to 600 mg daily and further to 300 mg daily after the first month, or discontinued temporarily or permanently, in patients who develop serious adverse effects. Treatment with BPaL is normally given for 6 to 9 months.

Children over 5 kg bodyweight and up to 14 years of age

Dosage for children receiving longer regimens for MDR-TB is based on body weight.

Children weighing more than 45 kg may be given the adult dose of 1 tablet (600 mg) daily.

Patients under 15 years of age and weighing 45 kg or less should be given other formulations to allow appropriate dosage, e.g. an oral suspension containing 20 mg/mL or dispersible tablets containing lower amounts of linezolid.

If such formulations are not available, an extemporaneous preparation may be prepared from a single 600-mg tablet of [TB323 trade name] in 10 mL of drinking water in order to facilitate administration in patients

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

in lower weight-bands and avoid fractioning solid formulations, although bioavailability is uncertain. This preparation supplies the following doses:

Child's weight	Volume (dose) of extemporaneous solution to be given	Equivalent to
5-15 kg	2.5 mL daily	150 mg daily
16-34 kg	5 mL daily	300 mg daily[1]
35-45 kg	7.5 mL daily	450 mg daily

[1] Children in this weight band able to swallow tablets can take the dose as half (0.5) tablet.

For detailed instructions, see section 6.6.

[TB323 trade name] is not recommended for use in children with a body weight less than 5 kg.

Special populations

Elderly

No dose adjustment is required (see section 5.2).

Renal Impairment

No dose adjustment is required, including in patients with severe renal impairment (CLCR < 30 mL/min) (see sections 4.4 and 5.2). Due to the unknown clinical significance of higher exposure (up to 10 fold) to the two primary metabolites of linezolid in patients with severe renal insufficiency, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

As approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by haemodialysis, 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. Linezolid should, therefore, be used with special caution in patients with severe renal insufficiency who are undergoing dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

To date, 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 administered with caution to patients with liver dysfunction and only be used in such patients when the anticipated benefit is considered to outweigh the theoretical risk (see sections 4.4 and 5.2).

Method of administration

The recommended dose should be administered orally and the tablets should be swallowed whole.

[TB323 trade name] may be taken with food or between meals.

For instructions on preparing an extemporaneous formulation for children, see section 6.6.

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 medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any such medicinal product.

Unless there are facilities available for close observation and monitoring of blood pressure, linezolid must 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 syndrome, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
- Patients taking any of the following medications: 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.

Linezolid is contraindicated in women who are breastfeeding unless the benefits of therapy to the mother and breastfeeding to the child outweigh the risks (see section 4.6).

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 adverse effects were on some occasions reversible with lowering the dose of drug (usually from 600 mg daily to 300 mg daily). Haematologic toxicities are more frequent and severe after more than 28 days of treatment but are less common with current strategies of once-daily dosing.

Elderly patients treated with linezolid 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.

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 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.

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 it is considered absolutely necessary to continue therapy, 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.

In patients receiving high-dose linezolid (1200 mg daily) in combination with bedaquiline and pretomanid (BPaL regimen) who develop myelosuppression, consideration may be given to reducing dosage to 600 or 300 mg daily after the first month of treatment, or temporarily discontinuing the medicine (for up to 35 days). In particular, decreases in haemoglobin of more than 10% from baseline in the first 4 weeks of treatment should trigger a reduction in the dose of linezolid; haemoglobin levels generally recover after dose reductions.

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

Lactic acidosis

Lactic acidosis has been reported with the use of linezolid. 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 should receive immediate medical attention. If lactic acidosis occurs, the benefits of continued use of 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, ongoing 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 spontaneous 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 and serotonergic agents, such as serotonin re- uptake inhibitors, tricyclic antidepressants and serotonin 5-HT_1 receptor agonists (triptans), should not usually be co-administered (see section 4.3), except where administration of both is 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 early signs or symptoms occur healthcare providers should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation 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 with cessation of drug. The outcome of optic neuropathy upon cessation of linezolid is less clear, and should be treated as a medical emergency.

If possible, patients' visual function should be regularly monitored. Ophthalmologic examination should include tests for black-white/chromatic visual acuity (e.g. Snellen eye chart and 65-test) and ophthalmoscopy and should be repeated for any suspicion of change in acuity or colour vision. 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 peripheral or optic neuropathy occurs, the continued use of linezolid should be weighed against the potential risks. In patients receiving high-dose linezolid (1200 mg daily) in combination with bedaquiline and pretomanid (BPaL regimen) who develop peripheral neuropathy after the first month of treatment, consideration may be given to reducing dosage to 600 or 300 mg daily, or temporarily discontinuing the medicine (for up to 35 days).

Convulsions

Convulsions have been reported to occur in patients when treated with linezolid. In most of these 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); however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid must not be used with certain medicines (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) and should not be used with some other medicines or in circumstances where MAO inhibition may be a risk unless close observation and monitoring is possible (see sections 4.3 and 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 therapy on normal flora have not been evaluated in clinical trials.

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

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

Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans; possible effects of linezolid on the human male reproductive system are not known (see section 5.3). The potential risk of reduced male fertility should be taken into account when treating adolescents and post-pubertal boys.

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 healthy volunteers, linezolid enhanced the increases in blood pressure caused by ***pseudoephedrine*** and ***phenylpropanolamine hydrochloride***. Co-administration of linezolid with either pseudoephedrine or phenylpropanolamine resulted in mean increases in systolic blood pressure of the order of 30-40 mmHg, compared with 11-15 mmHg increases with linezolid alone, 14-18 mmHg with either pseudoephedrine or phenylpropanolamine alone and 8-11 mmHg with placebo. Similar studies in hypertensive subjects 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 drug-drug 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 (MAOI). There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients on concomitant medications (e.g. ***phenelzine, isocarboxazid, selegiline, moclobemide***) that might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see sections 4.3 and 4.4).

Use with tyramine-rich foods

No significant pressor response was observed in subjects 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).

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.

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). Similarly, 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 sixteen 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 linezolid C_{max} and AUC by a mean 21% [90% CI, 15, 27] and a mean 32% [90% CI, 27, 37], respectively. 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, if any, of these findings.

4.6 Fertility, pregnancy and breastfeeding

Pregnancy

There are limited data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). A potential risk for humans exists.

Linezolid should not be used during pregnancy unless clearly necessary, i.e. only if the potential benefit outweighs the possible risk.

Breastfeeding

Linezolid is excreted 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 breastfed infant; however, diarrhoea and vomiting were the most common adverse reactions reported in clinical trials in infants receiving linezolid therapeutically.

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from [TB323 trade name] therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

In animal studies, linezolid caused a reduction in 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, a risk of reduced fertility cannot be ruled out, specifically with long-term treatment in male adolescents.

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

The majority of available safety data on linezolid does not come from patients with tuberculosis but has been generated in patients with other conditions using higher doses of linezolid for less than four weeks.

Adverse events

The most commonly reported adverse reactions are diarrhoea, headache, nausea and vomiting. About 3% of patients discontinued treatment because they experienced a drug-related adverse event.

The adverse reactions listed below, arranged by system organ class, use 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).

System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Infections and infestations	candidiasis, oral; candidiasis, vaginal; candidiasis; fungal infections	vaginitis	antibiotic-associated colitis, including pseudomembranous colitis*		
Blood and the lymphatic system disorders	anaemia*†	leukopenia*; neutropenia; thrombocytopenia*; eosinophilia	pancytopenia*		myelosuppression; sideroblastic anaemia*
Immune system disorders					anaphylaxis
Metabolic and nutrition disorders		hyponatraemia			lactic acidosis*
Psychiatric disorders	insomnia				
Nervous system disorders	Headache; taste perversion (metallic taste); dizziness	convulsions*; hypoaesthesia; paraesthesia			serotonin syndrome**; peripheral neuropathy*
Eye disorders		blurred vision*	changes in visual field (defect)*		optic neuropathy*; optic neuritis*; loss of vision*; changes in visual acuity*; changes in colour vision*
Ear and labyrinth disorders		tinnitus			
Cardiac disorders		arrhythmia (tachycardia)			
Vascular disorders	hypertension†	Transient ischaemic attacks†;			
Gastrointestinal disorders	diarrhoea, nausea, vomiting, localised or general abdominal pain†, constipation, dyspepsia	pancreatitis; gastritis; abdominal distention; dry mouth; glossitis; loose stools; stomatitis; tongue discoloration or disorder	superficial tooth discoloration		
Hepatobiliary disorders	abnormal liver function test; increased AST, ALT or alkaline	increased total bilirubin			

	phosphatase				
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria; dermatitis; diaphoresis			bullous disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis; angioedema; alopecia
Renal and urinary disorders	increased BUN	renal failure; increased creatinine; polyuria			
Reproductive system and breast disorders		vulvovaginal disorder			
General disorders and administration site conditions	fever	chills; fatigue; increased thirst			
Investigations	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.	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 program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for >28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for >28 days.

A meta-analysis of longer-term tuberculosis regimens included experience from over 300 patients who were treated with linezolid for at least 1 month, mostly at a dose of 600 mg/day. About 30% only received linezolid for 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 BPaL regimen of 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

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Health care providers are asked to report any suspected adverse reactions to the marketing authorisation holder, or, if available, via the national reporting system.

4.9 Overdose

Symptoms

No cases of overdose have been reported. Signs of toxicity in rats following 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.

Supportive care is advised together with maintenance of glomerular filtration. Approximately 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 *in-vitro* activity against aerobic Gram positive bacteria and anaerobic micro-organisms. 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 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 minimum inhibitory concentration (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

Linezolid's mechanism of action differs from those of other antibiotic classes. *In-vitro* studies with clinical isolates (including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and penicillin- and erythromycin-resistant streptococci) indicate that linezolid is usually active against organisms which are resistant to one or more other classes of antimicrobial agents.

As documented with other antibiotics when used in patients with difficult to treat infections and/or for prolonged periods, emergent decreases in susceptibility have been observed with linezolid.

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 found to be related to mutations in the 23S rRNA and mutation T460C in *rplC*, encoding the 50S ribosomal L3 protein. In addition, data are suggestive of a nonribosomal 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, individually based chemotherapy regimen with or without linezolid (starting dose of 1200 mg/day for a period of 4–6 weeks followed by a dose of 300-600 mg/day). Treatment duration ranged from 6 to 24 months with an average of ~12 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<.001). Treatment success rates were 69.7% (23/33) and 34.4% (11/32) in the linezolid group and control group, respectively (p=0.004).

Another randomised controlled trial enrolled 41 patients with sputum-culture–positive extensively drug-resistant tuberculosis who did not respond to any available chemotherapeutic option 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 randomized to continued 600 mg/day or 300 mg/day linezolid therapy 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.

An open-label, single-group study involving 109 patients with extensively drug-resistant tuberculosis or multidrug-resistant tuberculosis that was not responsive to treatment or could not be managed with second-line treatment due to side effects, looked at the effect of a regimen of high dose linezolid together with bedaquiline and pretomanid (BPaL regimen). As part of the regimen, patients were given oral linezolid 1200 mg daily for up to 26 weeks, reduced if necessary after the first month to 600 mg and then 300 mg daily, depending on side effects. A favourable outcome (resolution of clinical disease and negative sputum-culture) was seen in 98 patients on follow-up for 6 months after the end of treatment; 11 patients had bacteriological or clinical treatment failure (defined as change from protocol due to lack of efficacy, retreatment for tuberculosis, or tuberculosis-related death).

5.2 Pharmacokinetic properties

As [TB323 trade name] met the WHO criteria for a BCS-based biowaiver, a bioequivalence study was not conducted. Therefore, no pharmacokinetic data are available for this product.

Comparability between the WHO-accepted comparator product and [TB323 trade name] regarding the qualitative and quantitative composition of the formulations have been sufficiently proven.

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 in exposure to the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e. creatinine clearance < 30 ml/min). However, there was no increase in AUC of parent drug. 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 following dialysis than those observed 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 seen in 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 would not be 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 600mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that observed 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, variable cerebrospinal fluid (CSF) linezolid concentrations were observed following either single or multiple dosing of linezolid. Therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empirical treatment of paediatric patients with central nervous system infections is not recommended.

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 approximately 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 substantially rise above those known to be well tolerated and, 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 further special hazard mentioned below for humans. 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 excreted into the milk of lactating rats and the concentrations observed were higher than those in maternal plasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core tablet: maize starch
sodium starch glycolate
microcrystalline cellulose
hydroxypropyl cellulose
magnesium stearate

Film coat: hypromellose
titanium dioxide
macrogol/polyethylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

60 months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

[TB323 trade name] is available in aluminium-aluminium strip packs containing either 4 or 10 tablets. Pack sizes: carton with 1 strip of 4 tablets (1x4); carton with 10 strips of 10 tablets (10x10).

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.

Preparation and administration - extemporaneous formulation for children

Two small bowls, drinking water, a teaspoon and an oral syringe are needed for preparing the extemporaneous formulation. The following steps should be applied:

1. One 600-mg tablet should be disintegrated in a small bowl in 10 mL of drinking water by stirring gently.
2. The required portion of the mixture (see dosing table above) should be withdrawn with the syringe.
3. The withdrawn mixture should be mixed with additional liquid or semi-solid food to improve palatability.
4. The mixture should be administered immediately to the child.
5. Any unused mixture must be discarded.

7. SUPPLIER

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8. WHO REFERENCE NUMBER (WHO Prequalification Programme)

TB323

9. DATE OF PREQUALIFICATION

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10. DATE OF REVISION OF THE TEXT

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References

This text is primarily based on the SmPC for Zyvox 600 mg Film-Coated Tablets, available at: https://www.medicines.org.uk/emc/product/1688/smpc (accessed 21 May 2019)

WHO consolidated guidelines on tuberculosis, Module 4: Treatment Drug-resistant tuberculosis treatment 2020. Available at: https://apps.who.int/iris/bitstream/handle/10665/332397/9789240007048-eng.pdf

WHO operational handbook on tuberculosis: module 4: treatment: drug-resistant tuberculosis treatment (2020), Available at: https://apps.who.int/iris/bitstream/handle/10665/332398/9789240006997-eng.pdf

Mirzayev F, Viney K, Linh NN, et al. World Health Organization recommendations on the treatment of drug-resistant tuberculosis, 2020 update. Eur Respir J 2020; in press. Available at: https://doi.org/10.1183/13993003.03300-2020

WHO consolidated guidelines on drug-resistant tuberculosis treatment (2019), World Health Organization, Geneva. Available at: https://www.who.int/tb/publications/2019/consolidated-guidelines-drug-resistant-TB-treatment/en/ (accessed 21 May 2019)

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