SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Linezolid Tablets 600 mg

LINESPAN-600

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains:
Linezolid……..600 mg

Colour: Titanium Dioxide

3. PHARMACEUTICAL FORM

Tablet

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Linezolid 600 mg Tablets is indicated in combination with other anti tuberculosis agents for the treatment of tuberculosis caused by *Mycobacterium tuberculosis* in adults and adolescents weighing ≥30 kg.
Linezolid 600 mg Tablets is only indicated as a second-line antimycobacterial drug when use of first-line drugs is not appropriate due to resistance or intolerance (see sections 4.2, 4.4 and 5.1).

Consideration should be given to official treatment guidelines for tuberculosis, e.g. those of WHO: *http://www.who.int/tb/MDRTBguidelines2016.pdf*

4.2 Posology and method of administration

Posology

Adults and adolescents aged 12 years and older and weighing ≥30 kg

The dose of Linezolid 600 mg Tablets is one 600 mg tablet once daily. The dose may be reduced to 400-300 mg/day if serious adverse effects develop (see sections 4.4 and 4.8).

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 (CL_{CR} < 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).

Paediatric population

Reduction in fertility of males was observed in animal studies (see sections 4.4, 4.6 and 5.3). The potential risk of reduced male fertility should be taken into account when treating adolescents.
Linezolid 600 mg Tablets is not recommended for use in children below the age of 12 years and with a body weight <30 kg. The recommended dose is 10 mg/kg, three times daily, which cannot be achieved with this formulation.

Method of administration

The recommended dose should be administered orally.
Linezolid 600 mg Tablets may be taken with food or between meals.
For patients not able to swallow the tablets whole, the tablets may be crushed and added to a small amount of semi-solid food or liquid, all of which should be consumed immediately.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
Linezolid should 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 should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medications:

- Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
- Patients taking any of the following medications: serotonin re-uptake inhibitors (see section 4.4), tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

Linezolid is contraindicated in women who are breastfeeding (see section 4.6).

4.4 Special warnings and special precautions for use

Given the potentially serious adverse effects of linezolid – particularly anaemia, thrombocytopenia, lactic acidosis, peripheral neuropathy and optic neuropathy - the decision to use linezolid must balance its risks and benefits and the availability of other TB medicines. Due to the potential for severe and life threatening adverse events, close monitoring is strongly advised. Where this is not possible, linezolid is best reserved for MDR-TB patients who have additional drug resistance, or XDR-TB, or who are intolerant to other components of the core regimen.

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 less common with current strategies of once-daily dosing. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pretreatment levels. The risk of these effects appears to be related to the duration of treatment. 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. Close monitoring of complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) is recommended in patients who receive linezolid. 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; or 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 addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count.

Post marketing reports and compassionate use studies showed a higher incidence of serious anaemia in patients receiving linezolid for longer than 28 days. These patients more often required blood transfusion.

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 *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, serotonin 5-HT_1 receptor agonists (triptans), should not usually be co-administered (see section 4.3), except where administration of linezolid and concomitant serotonergic agents is essential. In those cases patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur 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; these reports have primarily been in patients treated for longer than 28 days. 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. Sellen 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.

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 healthcare 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 (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) which might put them at risk from MAO inhibition. Therefore, linezolid should not be used in these circumstances 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. For example, approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. 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 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 sections 4.2, 4.6 and 5.3).

Potential interactions producing elevation of blood pressure

Linezolid can enhance increases in blood pressure caused by drugs with a vasopressive 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.

Clinical trials

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

Controlled clinical trials did not include patients with diabetic foot lesions, decubitus or ischaemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

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 vasopressive action, unless concomitant use is essential. It is recommended that doses of directly and indirectly acting sympathomimetic agents (including adrenergic bronchodilators), vasopressive agents (e.g. epinephrine, norepinephrine), 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 serotonin re-uptake inhibitors, tricyclic antidepressants, 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).

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 lactation

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. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with Linezolid 600 mg Tablets.

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. 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 (see section 4.2).

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

Of note, the majority of available safety data on linezolid has been generated in patients with other conditions than tuberculosis in studies using higher doses of linezolid with a duration of 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 following adverse reactions have been observed and reported during treatment with linezolid with the following frequencies: common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), 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, phlebitis, thrombophlebitis			

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System Organ Class	Common	Uncommon	Rare	Very Rare	Not known
Gastrointestinal disorders	diarrhoea, nausea, vomiting, localized 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 phosphatase	increased total bilirubin			
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria, dermatitis, diaphoresis			bullous disorders such as those described 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, localized pain	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 sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride. Haematology Increased reticulocyte count. Decreased neutrophils.			

* See section 4.4
** See sections 4.3 and 4.4
† See below

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.

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. Healthcare 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 randomized 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 randomized 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.

5.2 Pharmacokinetic properties

Absorption and bioavailability

After oral administration, linezolid is rapidly and extensively absorbed. Absolute oral bioavailability of linezolid is complete (approximately 100%) as compared to intravenous administration.

No bioequivalence study has been performed. As linezolid is selected by the WHO being eligible for a BCS based biowaiver, a request for a biowaiver has been made. In accordance with the WHO guidance and criteria for biowaivers, supporting data have been provided regarding formulation comparability and in vitro dissolution data.

Comparability between the reference Zyvox® 600 mg tablet (Pfizer Limited) and the test Linezolid 600 mg Tablets (Cipla Limited, India) regarding the qualitative and quantitative composition of the formulations have been sufficiently proven. In addition, comparable in vitro dissolution at a pH 1, 4.5 and 6.8 have been shown. Accordingly, the test Linezolid 600 mg Tablets (Cipla Limited, India) meets the criteria for a BCS based biowaiver and is therefore considered bioequivalent to the reference Zyvox® 600 mg tablet (Pfizer Limited).

Steady state conditions are achieved by the second day of dosing.

Oral absorption is not significantly affected by food intake.

Distribution

Volume of distribution at steady-state averages at about 40-50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31% and is not concentration dependent.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in volunteer studies following multiple dosing. The ratio of linezolid in saliva and sweat relative to plasma was 1.2:1.0 and 0.55:1.0, respectively. The ratio for epithelial lining fluid and alveolar cells of the lung was 4.5:1.0 and 0.15:1.0, when measured at steady-state C_{max}, respectively. In a small study of subjects with ventricular-peritoneal shunts and essentially non-inflamed meninges, the ratio of linezolid in cerebrospinal fluid to plasma at C_{max} was 0.7:1.0 after multiple linezolid dosing.

Biotransformation

Linezolid is primarily metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives; the aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite (PNU-142586). The hydroxyethyl glycine metabolite (PNU-142586) is the predominant human metabolite and is believed to be formed by a non-enzymatic process. The aminoethoxyacetic acid metabolite (PNU-142300) is less abundant. Other minor, inactive metabolites have been characterised.

Elimination

Linezolid is primarily excreted under steady-state conditions in the urine as PNU-142586 (40%), parent drug (30%) and PNU-142300 (10%). Virtually no parent drug is found in the faeces whilst approximately 6% and 3% of each dose appears as PNU-142586 and PNU-142300, respectively. The elimination half-life of linezolid averages at about 5-7 hours.

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

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 (see sections 4.2 and 4.4).

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 (see sections 4.2 and 4.4).

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 10mg/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

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those in humans. 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. Supplementation of testosterone had no effect on linezolid-mediated fertility effects. Epididymal hypertrophy was not observed in dogs treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 times or equivalent, respectively, to those in humans. The same linezolid concentrations caused maternal toxicity in mice and were related to increased embryo death including total litter loss, decreased foetal body weight and an exacerbation of the normal genetic predisposition to sternal variations in the strain of mice. In rats, slight maternal toxicity was noted at exposures lower than clinical exposures. Mild foetal toxicity, manifested as decreased foetal body weights, reduced ossification of sternebrae, reduced pup survival and mild maturational delays were noted. When mated, these same pups showed evidence of a reversible dose-related increase in pre-implantation loss with a corresponding decrease in fertility. In rabbits, reduced foetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) at low exposure levels 0.06 times compared to the expected human exposure based on AUCs. The species is known to be sensitive to the effects of antibiotics.

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

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 1 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.

Preclinical data, based on conventional studies of repeated-dose toxicity and genotoxicity, revealed no further special hazard for humans. Carcinogenicity / oncogenicity studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline cellulose
Starch
Sodium starch glycolate
Hydroxy propyl cellulose
Magnesium stearate
Opadry white 85F28751
Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

Carton containing ALU-PVC Blister of 10 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. MARKETING AUTHORISATION HOLDER AND MANUFACTURER

Cipla Ltd., India

8. MARKETING AUTHORISATION NUMBER(S)

09/218783

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

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10. DATE OF REVISION OF TEXT

Sept 2017

Cipla