Summary of the Product Characteristics (SmPC)

1. Name of the medicinal Product

Linezolid Tablets 600 mg

2. Qualitative and Quantitative Composition

Qualitative declaration

Linezolid USP

Quantitative declaration

For full list of Excipients, see section 6.1.

3. Pharmaceutical Form

Oral Dosage Form, Tablets

White to off-white coloured, capsule shaped, biconvex, plain on both sides of film coated tablets.

Distribution Category: POM

4. Clinical Particulars

4.1 Therapeutic Indications

Nosocomial pneumonia, Community acquired pneumonia: It is indicated in adults for the treatment of community acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram positive bacteria. In determining whether Linezolid is an appropriate treatment, the results of microbiological tests or information on the prevalence of resistance to antibacterial agents among Gram positive bacteria should be taken into consideration. It is not active against infections caused by gram negative pathogens. Specific therapy against Gram negative organisms must be initiated concomitantly if a gram negative pathogen is documented or suspected. complicated skin and soft tissue infections.

Linezolid is indicated in adults for the treatment of complicated skin and soft tissue infections only when microbiological testing has established that the infection is known to be caused by susceptible gram positive bacteria.

It is not active against infections caused by gram negative pathogens. Linezolid should only be used in patients with complicated skin and soft tissue infections with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available in these circumstances treatment against gram negative organisms must be initiated concomitantly.

Linezolid should only be initiated in a hospital environment and after consultation with a relevant specialist such as a microbiologist or infectious diseases specialist.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Summary of the Product Characteristics (SmPC)

4.2 Posology and Method of Administration

Method of administration: The recommended linezolid dosage should be administered orally twice daily taken with or without food.

Recommended dosage and duration of treatment for adults:

The duration of treatment is dependent on the pathogen, the site of infection and its severity, and on the patient's clinical response. The following recommendations for duration of therapy follow.

Shorter treatment regimens may not be suitable for some types of infection. The maximum treatment duration is 28 days.

The safety and effectiveness of linezolid have not been established. No increase in the recommended dosage or duration of treatment is required for infections associated with concurrent bacteraemia.

The dose recommendation for the tablets for orally identical as follows:

Nosocomial pneumonia, Community acquired pneumonia and Complicated skin and soft tissue infections: 600 mg, twice daily, duration: 10-14 Consecutive days.

Paediatric population: Not Recommended, the safety and efficacy of linezolid in children aged (< 18 years old) has not been established.

Elderly: No dose adjustment is required.

Renal impairment: No dose adjustment is required

Severe renal impairment (i.e. CLCR <30 mUmin): No dose adjustment is required.

4.3 Contraindications

Hypersensitivity to linezolid or its components or to any of the excipients. 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, acuteconfusional states.

4.4 Special Warnings and Special Precautions for Use:

Patients should not be take or avoid linezolid with administered with the concomitant medication which may contradict occur underlying clinical conditions. (i.e serotonin re-uptake inhibitors, 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 should be administered to such patients only when close monitoring blood pressure, haemoglobin levels, blood counts and platelet counts is possible.

Myelosuppression: (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. 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. Therefore, close monitoring of blood counts is recommended in patients who: have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 10-14 days of therapy.

Mortality imbalance in established data in patients with catheter-related Gram positive bloodstream infections: Excess mortality may occur in patients treated with linezolid, relative to vancomycin/dicloxacillin/oxacillin.

Antibiotic-associated diarrhoea and antibiotic-associated colitis: including pseudomembranous colitis and Clostridium difficile-associated diarrhoea, has been reported in association with the use of nearly all antibiotics including linezolid.

Lactic acidosis: Lactic acidosis has been reported with the use of linezolid (signs and symptoms of metabolic acidosis) If lactic acidosis occurs, the benefits of continued use of linezolid should be weighed against the potential risks.

Mitochondrial dysfunction: it 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: Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, If signs or symptoms occur physicians should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur.

Peripheral and optic neuropathy, as well as optic neuropathy and optic neuritis sometimes progressing to loss of vision, have been reported in patients trea1ed with linezolid these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days.

Convulsions: it may be reported to occur in patients when treated with linezolid. In most of these cases, a history of seizures may occur. Patients should be advised to inform their physician if they have a hi story of seizures.

Monoamine oxidase inhibitors: it 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. Linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible. Patients should be advised against consuming large amounts of tyramine-rich foods.

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. Patients use cautionly it may occur super infection during therapy, appropriate measures should be taken.

Special populations:

Renal impairment: 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.

Hepatic impairment: No dose adjustment is required. It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk.

Impairment of fertility: Linezolid reversibly decreased fertility and induced abnormal sperm possible effects of linezolid on the human male reproductive system are not known.

Paediatric population (< 18 years old): There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old) and therefore, use of linezolid in this age group is not recommended.

Pregnancy: There are limited data from the use of linezolid in pregnant women. Linezolid should not be used during pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the theoretical risk.

Lactation: Breast-feeding: its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration.

4.5 Interaction with other medicinal products and other forms of interaction

Linezolid can cause serious interactions with many common drugs: MO inhibitors: It 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. Potential interactions producing elevation of blood pressure: Pseudoephedrine: increased risk of hypertension and associated adverse effects. Potential serotonergic interactions: serotonin syndrome: linezolid with serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), Therefore, while co-administration is contraindicated, management of patients for whom treatment with linezolid and serotonergic agents is essential. Drug-food: Tyramine-containing foods and beverages (such as beer; Chianti and certain other red wines; aged cheese; bananas; aged, cured, or spoiled meats; salted herring and other dried fish;

avocado; bean curd; red plums; soy sauce; spinach; tofu, tomatoes; yeast). 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. Antiplatelet drugs (such as aspirin, dipyridamole, and nonsteroidalanti-inflammatory drugs): increased bleeding risk. Drug-diagnostic tests. Prothrombin time: altered Rifampicin: The mechanism of this interaction and its clinical significance are unknown. Warfarin: There are insufficient data from patients who have received warfarin and linezolid to assess the clinical significance. When warfarin was added to linezolid therapy at steadystate, there was a 10% reduction in mean maximum INRon Coad ministration with a 5% reduction in AUC INR.

4.6 Pregnancy and Lactation

Pregnancy: There are limited data from the use of linezolid in pregnant women. Linezolid should not be used during pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the theoretical risk.

Lactation: Breast-feeding: its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration.

Fertility: In animal studies, linezolid caused a reduction in fertility. It is not known whether these findings have an impact on human fertility.

4.7 Effects on ability To Drive and use Machines

Patients should be warned about the potential for dizziness or symptoms of visual impairment whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8 Undesirable Effects

The most commonly patients taking linezolid they cause diarrhoea, headache, nausea and vomiting. Infections and infestations: candidiasis, oral candidiasis, vaginal candidiasis, fungal infections, Vaginitis, antibiotic associated colitis, including pseudomembranous colitis. Blood and the lymphatic system disorders: anaemia, leucopenia, neutropenia, thrombocytopenia, eosinophilia, pancytopenia, myelosuppression, sideroblastic anaemia. Immune system disorders: anaphylaxis. Metabolism and nutrition disorders: hyponatraemia, lactic acidosis. Psychiatric disorders: insomnia: and CNS disorder: anxiety, confusion, difficulty speaking, dizziness, hallucinations, lethargy, paresthesia, light-headedness, fatigue, drowsiness, headache, seizures.

Eye disorders: blurred vision, Ear and labyrinth disorders: tinnitus, Cardiac disorders: arrhythmia (tachycardia). Vascular disorders: hypertension, Gastrointestinal disorder: nausea, vomiting, diarrhea, gastritis, anorexia, dry mouth, pseudomembranous coli tis, Hepato-biliary disorders: abnormal liver function test; increased ASTALT or alkaline phosphatase. Skin and subcutaneous tissue disorders: Skin: rash, photosensitivity,

diaphoresis, other fungal infections. Renal and urinary disorders: increased BUN, renal failure. 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. Increased sodium or calcium. Decreased non-fasting glucose. Increased or decreased chloride. Haematology: Increased reticulocyte count. Decreased neutrophils.

4.9 Overdose

Symptoms: Symptoms occur may be ataxia, vomiting, tremors. No specific antidote is known.

Signs of toxicity nonclinical following doses of 3000 mg/kg/day linezolid were decreased activity, 2000 mg/kg/day.

Treatment: No cases of overdose have been reported. However, the following information may prove useful: 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 Pharmacodynamics Properties

Pharmacological catogary: Other antibacterials (oxazolidinones)

ATC Code: J01XX08

Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. Linezolid's mechanism of action differs from those of other antibiotic classes. It has in vitro activity against aerobic Gram positive bacteria and anaerobic micro-organisms. It selectively inhibits bacterial protein synthesis via a unique mechanism of action. Specifically, it binds 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.

Breakpoints: On the basis of microbiological, Pharmacological and clinically define as susceptible bacterial isolates with linezolid MICs for Staphylococcus sp. as susceptible at 4 mcg/mL or less and resistant at 8 mcg/mL or more. The MICs are defined for Enterococcus sp. as susceptible at 2 mcg/mL or less, intermediate at 4 mcg/mL (based on the known ability of linezolid to concentrate in the urine), and resistant at 8 mcg/mL or more.

The MICs are defined for S. pneumoniae, beta-hemolytic Streptococcus sp., and S. viridans group as susceptible at 2 mcg/mL or less.

Susceptibility: The susceptibility interpretive criteria for linezolid are delineated by pathogen. Linezolid is also a reversible, non-selective inhibitor of monoamine oxidase (MAO).

Resistance: It resistance in Gram-positive cocci has been encountered clinically as well as in vitro, but it is still a rare phenomenon. The resistance to this antibiotic has been, until now, entirely associated with distinct nucleotide substitutions in domain V of the 23S rRNA genes.

Cross resistance: It differs from those of other antibiotic classes. Bacterial 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. When antibiotic-resistant organisms are encountered in the hospital it is important to emphasize infection control policies.

5.2 Pharmacokinetic Properties

It is primarily contains (s)- linezolid which is biologically active and is metabolised to form inactive derivatives.

Absorption: it is orally rapid and extensively absorbed. Plasma C_{max}, reached within 2 hours. Absolute oral bioavailability of is complete (approximately 100%). It is not significantly affected by food and absorption. It steady-state follow oral twice daily 600 mg of dose. Plasma C_{max} and C_{min} (mean: 21.2 [SD 5.8] mg/1 and mean: 6.15 [SD 2.94] mg/l respectively, it achieved by the second day of dosing. **Distribution:** it is distribute in total body water, approx. 40-50 litres. Plasma protein binding: 3 1% and is not concentration dependent it determined in various fluids from follow multiple dosing. The ratio of linezolid in Saliva (1.2: 1.0), sweat (0.55: 1.0), Epithelial lining fluid (4.5: 1.0), alveolar cells of the lung (0.15: 1.0), variable cerebrospinal fluid (CSF) linezolid concentrations were observed following either single or multiple dosing of linezolid. **Biotransformation:** it 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 and the hydroxyethyl glycine metabolite. The hydroxyethyl glycine metabolite is the predominant human metabolite and is believed to be formed by a non-enzymatic process. The aminoethoxyacetic acid metabolite is less abundant. Other minor, inactive metabolites characterised. **Elimination:** In patients with normal renal function or mild to moderate renal insufficiency, it is primarily excreted in urine as (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 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 and hepatic impairment: Linezolid should be used with special caution in patients with severe renal insufficiency and patients with severe hepatic insufficiency only when the anticipated benefit is considered to outweigh the theoretical risk.

Impairment of fertility: Linezolid reversibly decreased fertility and induced abnormal sperm possible effects of linezolid on the human male reproductive system are not known.

Paediatric population (< 18 years old): There are insufficient data on the safety and efficacy of linezolid in children and adolescents(< 18 years old) and therefore, use of linezolid in this age group is not recommended. 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.

Susceptible organisms: Gram positive aerobes, gram positive anaerobes, resistant organisms resistance, cross resistance. Resistance to linezolid is associated with point mutations in the 23S rRNA. As accepted 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 has been reported in enterococci, Staphylococcus aureus and coagulase negative staphylococci. This generally has been associated with prolonged courses of therapy and the presence of prosthetic materials or undrained abscesses. When antibiotic-resistant organisms are encountered in the hospital it is important to emphasize infection control policies.

Information from clinical data in the paediatric population : The efficacy of linezolid (10 mg/kgq8h) was compared to vancomycin (10- 15mg/kgq6- 24h) in treating infections

due to suspected or proven resistant gram-positive pathogens (including nosocomial pneumonia, complicated skin and skin structure infections, catheter related bacteraemia, bacteraemia of unknown source, and other infections), in children from birth to 11 years. Quantifiable cure rates in the clinically evaluable for linezolid and vancomycin.

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 fetal 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 fetal toxicity, manifested as decreased fetal 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. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. 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 special hazard for humans beyond those addressed in other sections of this Summary of Product Characteristics. Carcinogenicity / oncogenicity studies have not been conducted in view of the short duration of dosing and lack of genotoxicity.

6. Pharmaceutical Particulars

6.1 List of Excipients

Microcrystalline Cellulose (Plain)
Hydroxy Propyl Cellulose (Klucel-LF)
Maize Starch
Sodium Starch Glycolate (Type A)
Magnesium Stearate
Opadry White YS-1-7040
Purified Water

Composition of Opadry white YS-1- 7040:

Hypromellose
Polyethylene Glycol/Macrogol
Titanium dioxide
Talc

6.2 Incompatibilities

Not applicable

6.3 Shelf Life

36 Months

6.4 Special Precautions for Storage

Do not store above 30°C. Protect from light.

6.5 Nature and Contents of Container

10 Tablets are packed in Alu-PVDC pack, Such 1 Blister are packed in a printed carton with packing insert.

6.6 Special precaution for disposal and other handling

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

7. Marketing Authorization Holder And Manufacturing Site Addresses

7.1 Name and Address of Marketing Authorization Holder

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

7.2 Name and Address of manufacturing site(s)

Lincoln Pharmaceuticals Limited
Trimul Estate, Khatraj, Taluka: Kalol,
District: Gandhinagar Gujarat, India.
Telephone no.: +91-79-41078096
Fax: +91-79-41078062
Email: hiren@lincolnpharma.com
Website: www.lincolnpharma.com

8. Marketing Authorization Number

TAN 22 HM 0377

9. Date of First <Registration> / Renewal of The <Registration>

21/09/2022

10. Date of Revision of the Text

-