SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LINEDOR 600 mg/300 ml I.V. solution for infusion, Vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Drug Substance:

Linezolid ..... 600 mg

Excipients:

Sodium citrate ..... 2.10 mg/ml

Sodium chloride ..... 9 mg/ml

Sodium hydroxide ..... 0.30 mg/ml

Glucose monohydrate ..... 50 mg/ml

For other excipients, see 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear, pale yellow, homogenous solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

LINEDOR is indicated for below mentioned infections caused by susceptible strains of microorganisms mentioned below. LINEDOR does not have clinical activity against Gram negative pathogens and is not indicated for the treatment of Gram negative infections. If a concomitant Gram negative pathogen is detected or suspected, a specific antibacterial therapy with Gram negative activity is required.

-Vancomycin-resistant *Enterococcus faecium* infections: Including cases with concurrent bacteremia.

-Nosocomial pneumonia: Caused by *Staphylococcus aureus* (methicillin-resistant and –susceptible strains) or *Streptococcus pneumoniae* (including multiple drug resistant strains [MDRSP])

-Complicated skin and soft tissue infections (including diabetic foot lesions, without concurrent osteomyelitis): Caused by *Staphylococcus aureus* (methicillin-resistant and –susceptible strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*. LINEDOR is indicated for complicated skin and soft tissue infections only when it's established with microbiological tests that infection is known to be caused by susceptible Gram positive bacteria. LINEDOR is not active against infections caused by gram negative pathogens. LINEDOR should only be used in complicated skin and soft tissue infections with known or possible co-infection with Gram negative organisms if there is no alternative treatment options available. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.
LINEDOR is not studied in patients with decubitus ulcer.

-Uncomplicated skin and soft tissue infections: Caused by *Staphylococcus aureus* (only methicillin-susceptible strains) or *Streptococcus pyogenes*.

-Community acquired pneumonia: Caused by *Streptococcus pneumoniae* (including multiple drug resistant strains [MDRSP] or *Staphylococcus aureus* (only methicillin-susceptible strains) including cases with concurrent bacteremia.

MDRSP indicates strains that are resistant to one or more of the antibiotics penicillin, second generation cephalosporins, macrolides, tetracycline and trimethoprim/sulfametoxazol.

4.2. Posology and method of administration

Posology/administration frequency and period:

Adults:

LINEDOR dose recommendations for infections are listed on the table below.

LINEDOR doses are administered every 12 hours. Adult patients with methicillin-resistant *Staphylococcus aureus* infections should be treated with LINEDOR 600 mg every 12 hours.

<table>
<tr><td colspan="4">Dosage chart for LINEDOR</td></tr>
<tr><td></td><td colspan="2">Dosage and route of administration</td><td>Recommended treatment duration</td></tr>
<tr><td>Infection*</td><td>Pediatric patients (Age 0-11)**</td><td>Adults and Adolescents (Age 12-18)</td><td></td></tr>
<tr><td>Vancomycin-resistant Enterococcus faecium infections including cases with concurrent bacteriemia</td><td>In every 8 hours

10 mg/kg IV or oral†</td><td>In every 12 hours

600 mg IV or oral†</td><td>14-28 days</td></tr>
<tr><td>Nosocomial pneumonia</td><td rowspan="3">In every 8 hours

10 mg/kg IV or oral†</td><td rowspan="3">In every 12 hours

600 mg IV or oral†</td><td rowspan="3">10-14 days</td></tr>
<tr><td>Complicated skin and soft tissue infections</td></tr>
<tr><td>Community-acquired pneumonia including cases with concurrent bacteriemia</td></tr>
<tr><td>Uncomplicated skin and soft tissue infections</td><td>Age <5: 10 mg/kg IV or oral† every 8 hours
Age 5-11: 10 mg/kg IV or oral† every 12 hours</td><td>Adults: 400 mg IV or oral† every 12 hours
Adolescents: 600 mg IV or oral† every 12 hours</td><td>10-14 days</td></tr>
<tr><td colspan="4">* Caused by indicated pathogens (see section 4.1. Therapeutic indications)</td></tr>
<tr><td colspan="4">† Oral use with linezolid film-coated tablet</td></tr>
<tr><td colspan="4">** Treatment for preterm newborns less than 7 days old (gestational age < 34 weeks) should be initiated with 10 mg/kg every 12 hours. If clinical response is insufficient dose increase to 10 mg/kg every 8 hours should be considered. In all newborns after the 7th day of birth, the dose should be 10 mg/kg every 8 hours.</td></tr>
</table>

In clinical studies the duration determined in the treatment protocol for all infections is 7-28 days. Total duration of the treatment is determined by clinician according to the infection site, severity and clinical response of the patient.

No dose adjustment is required when switched from intravenous administration to oral administration. Patients whose treatment is initiated with LINEDOR IV solution for infusion can be switched to linezolid film-coated tablets when clinically indicated by clinician.

Method of administration:

For intravenous administration. LINEDOR IV solution for infusion should be administered as intravenous infusion over a period of 30-120 minutes.

Additional information on special population:

Renal impairment:

No dose adjustment is required (see 5.2. Pharmacokinetic properties; 4.4. Special warnings and precautions for use).

Severe renal insufficiency (creatinine clearance < 30 ml/min): No dose adjustment is required. Due to the unknown clinical significance of higher exposure (up to 10 fold) to the two primary metabolites 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 LINEDOR dose is removed during the first 3 hours of hemodialysis, LINEDOR should be administered after dialysis in patients receiving such treatment. Although the primary metabolites of LINEDOR are removed to some extent by hemodialysis, the plasma the concentrations of these metabolites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore, LINEDOR should only be used in patients with severe renal insufficiencies who receive hemodialysis therapy, if the anticipated benefit is considered to outweigh the theoretical risk.

To date, there is no data available on the use of LINEDOR in patients receiving continuous ambulatory peritoneal dialysis (CAPD) or any other alternative treatment for renal insufficiency.

Hepatic impairment:

No dose adjustment is required. However there is limited clinical data and LINEDOR use is only recommended if anticipated benefit is considered to outweigh the theoretical risk (see 5.2. Pharmacokinetic properties; 4.4. Special warnings and precautions for use).

Pediatric population:

In pediatric patients LINEDOR dose is determined according to age and bodyweight (see section 4.2. Posology/administration frequency and period, Dosage chart for LINEDOR).

Geriatric population:

No dose adjustment is required (see 5.2. Pharmacokinetic properties; 4.4. Special warnings and precautions for use).

Other:

No dose adjustment is required regarding the gender.

4.3. Contraindications

LINEDOR is contraindicated in patients with hypersensitivity to linezolid or any of the excipients found in the formulation.

Monoamine Oxidase Inhibitors:

LINEDOR should not be used in patients taking any medicinal product which inhibits monoamine oxidase A or B (e.g. phenelzine, isocarboxazid) presently or in patients who took such medicinal product within two weeks.

Potential Interactions That May Cause High Blood Pressure:

Unless the patient's blood pressure is monitored, LINEDOR should not be used in patients with pheochromocytoma, thyrotoxicosis, uncontrolled hypertension, and/or in patients who take below

mentioned drugs: agents with direct or indirect sympathomimetic activity (e.g. pseudoephedrine, phenylpropanolamine), vasopressor agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine) (see. 4.5. Interaction with other medicinal products and other forms of interaction)

Potential Serotonergic Interaction:

LINEDOR should not be used in patients with carcinoid syndrome and/or in patients who take below mentioned drugs unless serotonin syndrome findings and/or symptoms in patients are carefully monitored: Serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5HT-1 receptor agonists (triptans), meperidine or buspirone (see 4.5. Interaction with other medicinal products and other forms of interaction)

4.4. Special warnings and precautions for use

Reversible myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid treatment was discontinued, the affected hematological parameters have risen towards pretreatment levels. Whole blood count should be monitored once a week in patients receiving linezolid, especially in those who received for more than 2 weeks, in patients with pre-existing myelosuppression, in those who concomitantly receive medication that causes myelosuppression and those who receive antibiotics before or concomitantly for chronic infection. If myelosuppression is developed or became severe discontinuation of linezolid therapy should be considered.

In an open-label study comparing linezolid with vancomycin/dicloxacillin/oxacillin in severely ill patients with intravascular catheter-related infections, mortality is found to be higher in patients who were treated with linezolid [78/363 (21.5%) vs 58/363 (16.0%)]. The main factor influencing the mortality rate was the Gram positive infection status at baseline. Mortality rates were similar in patients with infections caused only by Gram positive organisms (odds ratio 0.96; 95% confidence interval: 0.58-1.59), however it was significantly higher (p=0.0162) in patients in the linezolid treatment arm with any other pathogen or no pathogen at baseline (odds ratio 2.48, 95% confidence interval: 1.38-4.46). The greatest imbalance occurred during treatment and 7 days following discontinuation of the drug. More patients in the linezolid arm acquired Gram negative pathogens

during the study and died from infections caused by Gram negative pathogens and polymicrobial infections. Therefore, linezolid should be used in complicated skin and soft tissue infections with known or possible concomitant infections caused Gram negative organisms, only if there are no alternative treatment options available (see Section 4.1. Therapeutic indications). In these circumstances, treatment for Gram negative organisms should be initiated concomitantly.

LINEDOR is not clinicaly active against Gram negative pathogens and is not indicated for the treatment of Gram negative infections. If a concomitant Gram negative pathogen is detected or suspected, specific antibacterial therapy with Gram negative activity is required (see Section 4.1. Therapeutic indications).

Pseudomembranous colitis in various severities, from mild to life-threatening, is reported with almost all of the antibacterial agents (including linezolid). Therefore this diagnosis should be kept in mind in patients who present diarrhea subsequent to the administration of an antibacterial agent.

Clostridium difficile-associated diarrhea (CDAD) is reported with the administration of many antibacterial agents including linezolid and may vary from mild diarrhea to fatal colitis. Treatment with antibacterial agents causes overgrowth of *C. difficile* by changing colon's normal flora.

C. difficile produces A and B toxins causing CDAD. *C. difficile* strains overproducing toxins causes increased morbidity and mortality; these infections may be refractory to antimicrobial therapy and patients may need colectomy. CDAD possibility should be taken into consideration in patients developing diarrhea subsequent to administration of antibiotics. Medical history should be considered carefully since CDAD has been reported 2 months after the administration of any antibacterial agent.

Specific treatment should be initiated when CDAD is diagnosed. Generally mild CDAD cases respond only to discontinuation of the drug. Fluid and electrolyte treatment, protein supplementation and treatment with antibacterial agents with clinical activity against *Clostridium difficile* should be considered in moderate to severe cases.

Peripheral neuropathy and optic neuropathy have been reported in patients treated with linezolid. Most of these patients have been patients treated longer than the maximum recommended treatment duration of 28 days. In case of optic neuropathy causing loss of vision, patients were treated longer than the maximum treatment period. Peripheral and optic neuropathy cases were reported especially in patients treated with LINEDOR for more than 28 days. If peripheral and optic neuropathy develops, linezolid use should be weighed against potential risks.

If symptoms of visual impairment, such as visual acuity, changes in color vision, blurred vision or visual field defects develops immediate ophthalmic examination is recommended. Visual function should be monitored in all patients receiving linezolid for long periods (3 months or more) and in patients with new visual impairments regardless of the linezolid treatment period.

Lactic acidosis has been reported with the use of linezolid. If recurrent nausea or vomiting, unexplained acidosis or low bicarbonate levels are developed in patients receiving linezolid, patients should receive immediate medical attention.

Convulsions have been reported rarely in patients treated with linezolid. In most of these cases convulsion history or risk factors to cause convulsions have been reported.

Serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including selective serotonin re-uptake inhibitors (SSRI) has been reported.

In cases when the co-adminisrtation of LINEDOR and serotonergic agents is clinically essential, patients should be monitored closely for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs and symptoms occur, discontinuation of either one or both of the drugs should be considered. If concomitant use of serotonergic agent is withdrawn, discontinuation symptoms may be observed.

In healthy volunteers, 21% of decrease in C_{max} and 32% decrease in AUC has been observed with concomitant administration of linezolid with rifampin. Clinical significance of this interaction is not known.

The use of antibiotics may cause overgrowth of unsusceptible microorganisms. If superinfection occurs during treatment, appropriate measures should be taken.

LINEDOR should be used carefully in patients with uncontrolled hypertension, carcinoid syndrome or untreated hyperthyroidism.

This medicinal product contains 1262 mg sodium per vial. This should be taken into account in patients with controlled sodium diet.

This medicinal product contains 15 g glucose per vial. This should be taken into account in patients with diabetes mellitus.

4.5. Interaction with other medicinal products and other forms of interaction

In normotensive healthy volunteers, LINEDOR enhanced the increases in the blood pressure caused by pseudoephedrine and phenylpropanolamine. 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 on hypertensive subjects have not been conducted. It is recommended that the initial doses of drugs with a vasoconstrictive action, including dopaminergic agents, should be kept at low and should be carefully titrated to achieve the desired response.

<u>Drugs metabolized by cytochrome P450:</u>

Linezolid is not detectably metabolized by the human cytochrome P450 (CYP) enzyme system and it does not inhibit the activities of any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no interaction is expected between LINEDOR and the drugs induced by CYP450. Co-administration of LINEDOR does not significantly change pharmacokinetic properties of S-warfarin which is mostly metabolized by CYP2C9. Drugs that are CYP2C9 substrates, such as warfarin and phenytoin, can be used concomitantly with LINEDOR without a change in the dosage regimen.

Antibiotics:

Rifampin:

The effect of rifampin on the pharmacokinetics of linezolid has been studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days and rifampin 600 mg once daily for 8 days. Rifampin decreased the C_{max} and AUC of linezolid by a mean of 21% (90% CI, 15, 27) and a mean of 32% (90% CI, 27, 37), respectively. The mechanism of this interaction and its clinical significance are unknown.

Aztreonam:

Co-administration of LINEDOR and aztreonam does not change their pharmacokinetics.

Gentamycin:

Co-administration of LINEDOR and gentamycin does not change their pharmacokinetics.

Monoamine oxidase inhibition:

LINEDOR is a reversible, non-selective inhibitor of monoamine oxidase. Therefore there is a possibility of interaction with adrenergic and serotonergic agents.

Adrenergic agents:

A reversible increase in responses to sympathomimetic agents with indirect activity, to vasopressor or dopaminergic agents can occur in some of the patients receiving LINEDOR. Initial doses of adrenergic agents such as dopamine or adrenalin should be low and should be carefully titrated to achieve the desired response.

The drug interaction potential with dextromethorphan has been studied in healthy volunteers. No serotonin syndrome symptoms (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subject co-administered LINEDOR and dextromethorphan.

Alcohol should be avoided with the use of LINEDOR, for it may contain thyramine and therefore may cause hypertensive crisis.

Co-administering of LINEDOR with tramadol increases the risk of seizure.

Co-administering of LINEDOR with other myelosuppressive drugs increases the risk of myelosuppression.

Drug-laboratory test interactions:

No drug-laboratory test interaction has been reported.

Additional information on special population:

Renal/hepatic impairment:

No studies on interaction are available.

Pediatric population:

No studies on interaction are available

4.6. Pregnancy and lactation

General recommendation

Pregnancy category: C

Women who have childbearing potential/Birth Control (Contraception):

No sufficient data available on the use of linezolid in pregnant women.

Studies on animals have shown reproductive toxicity (see section 5.3. Preclinical safety data). A potential risk for humans exists.

Pregnancy period:

No sufficient controlled study available in pregnant women. LINEDOR should be used in pregnancy only if the anticipated benefit is considered to outweigh the possible risks.

No teratogenic effect was observed in the studies on rats and mice treated with linezolid. Mild fetal toxicity was observed in mice only on maternal toxic levels. In rats, fetal toxicity is manifested as decreased fetal body weight and reduced ossification of sternebrae (usually seen with decreased

body weight). This situation causes reduced pup survival and mild maturational delays. When mated, these same pups showed evidence of a reversible dose-related increase in pre-implantation loss.

Lactation period:

It is not known whether LINEDOR passes into breast milk. Animal data suggest that linezolid and its metabolites passes into breast milk. As many drugs passes into breast milk, LINEDOR should be used with caution in breastfeeding women. When deciding whether breastfeeding should be stopped or not or whether LINEDOR treatment should be discontinued or not/ treatment should be avoided or not, the benefit of breastfeeding to infant and the benefit of LINEDOR treatment to breastfeeding woman should be considered.

Reproduction/Fertility

In animal studies, a reduction in fertility caused by linezolid was observed in male rats.

4.7 Effects on ability to drive and use machines

The effect of LINEDOR on ability to drive and use machines has not been evaluated. Patients should be warned about the potential for dizziness whilst receiving LINEDOR and should be advised not to drive or operate machinery if dizziness occurs.

4.8. Undesirable effects

Frequency classification is defined as: very common (≥1/10); common (≥1/100 and <1/10); uncommon (≥1/1000 and <1/100); rare (≥1/10,000 and <1/1000); very rare (<1/10,000); unknown (cannot be estimated from the available data).

Provided data is based on the data from clinical studies that enrolled more than 2,000 adult patients who received the recommended linezolid doses for up to 28 days.

Adverse effects were reported in approximately 22% of the patients; those most commonly reported were headache (2.1%), diarrhea (4.2%), nausea (3.3%) and candidiasis (especially oral [0.8%] and vaginal [1.1%] candidiasis).

The most commonly reported drug-related adverse events which led to discontinuation of treatment were headache, diarrhea, nausea and vomiting. About 3% of patients discontinued treatment because they experienced a drug-related adverse event.

Infections and infestations

Common: Candidiasis (especially oral and vaginal candidiasis) or fungal infections, moniliasis

Uncommon: Vaginitis

Blood and the lymphatic system disorders

Uncommon: (frequency reported by clinicians): Eosinophilia, leukopenia, neutropenia, thrombocytopenia

Psychiatric disorders

Uncommon: Insomnia

Nervous system disorders

Common: Headache, taste perversion (metallic taste)

Uncommon: Dizziness, hypoesthesia, paraesthesia

Eye disorders

Uncommon: Blurred vision

Ear and labyrinth disorders

Uncommon: Tinnitus

Vascular disorders

Uncommon: Hypertension, phlebitis, thrombophlebitis

Gastrointestinal disorders

Common: Abdominal pain/cramps/abdominal distention, diarrhea, nausea, vomiting

Uncommon: Local or generalized abdominal pain, constipation, dry mouth, dyspepsia, gastritis, glossitis, loose stool, pancreatitis, tongue discoloration or disorder

Hepato-biliary disorders

Common: Abnormal liver function tests

Skin and subcutaneous tissue disorders

Uncommon: Dermatitis, diaphoresis, pruritus, rash, urticarial

Renal and urinary disorders

Uncommon: Polyuria

Reproductive system and breast disorders

Uncommon: Vulvovaginal disorder

General disorders and administration site conditions

Uncommon: Chills, fatigue, fever, injection site pain, increased thirst, localized pain

Investigations

Biochemistry:

Common: Increased AST, ALT, LDH, alkaline phosphatase, BUN, creatine kinase, lipase, amylase or non-fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate.

Uncommon: Increased total bilirubin, creatinine, sodium or calcium. Decreased non-fasting glucose. Increased or decreased chloride.

Hematology

Common: Increased neutrophils or eosinophils. Decreased hemoglobin, hematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.

Uncommon: Increased reticulocyte count. Decreased neutrophils

The following adverse reactions to linezolid were considered to be serious in rare cases: localized abdominal pain, transient ischemic attacks, hypertension, pancreatitis and renal failure.

In clinical studies, one case (tachycardia) related to the drug has been reported.

In controlled clinical trials where linezolid was administered for up to 28 days, anemia has been reported in less than 0.1% of the patients. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anemia 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 anemia and requiring blood transfusion was 9% (3/33) in patients treated with linezolid for ≤ 28 days and 15% (8/53) in those treated for >28 days.

Post-marketing experience

Blood and the lymphatic system disorders: Anemia, leucopenia, neutropenia, thrombocytopenia, pancytopenia, myelosuppression (see Section 4.4. Special warnings and precautions for use). In cases where anemia has been reported, patients requiring blood transfusion are higher in the group of patients receiving linezolid more than the recommended 28 days of maximum treatment period.

Immune system disorders: Anaphylaxis

Metabolism and nutrition disorders: Lactic acidosis (see Section 4.4. Special warnings and precautions for use).

Nervous system disorders: Peripheral neuropathy, convulsions, serotonin syndrome (see 4.4. Special warnings and precautions for use). Peripheral neuropathy has been reported in patients treated with linezolid. It has been reported mostly in cases when it’s administered longer than the maximum treatment period of 28 days.

Convulsions have been reported rarely in patients treated with linezolid. In most of these cases convulsion history or risk factors to cause convulsions have been reported.

Serotonin syndrome cases have been reported.

Eye disorders: Optic neuropathy causing loss of vision has been reported in patients treated with linezolid. Most of these reports belong to patients who were treated longer than the recommended period (28 day) (see 4.4. Special warnings and precautions for use).

Skin and subcutaneous tissue disorders: rash, angioedema. Very rarely, bullous disorders such as those described as Stevens-Johnson syndrome has been reported.

Gastrointestinal disorders: Tongue discoloration. Very rarely superficial tooth discoloration has been reported with linezolid use. This discoloration could be removed by professional teeth cleaning (manual scraping).

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions following registration is very important. Reporting enables the continuous follow-up of the beneficial/risk balance of the drug. Members of any health professions must report any suspected adverse reaction to Turkish Pharmacovigilance Centre (TÜFAM) (www.titck.gov.tr; e-mail: tufam@titck.gov.tr; Tel No: 0 800 314 00 08; Fax No: 0 312 218 35 99)

4.9 Overdose and treatment

No specific antidote is known.

In case of overdose, supportive care is advised together with maintenance of glomerular filtration. Hemodialysis may promote rapid elimination of linezolid. In a phase I clinical study, hemodialysis starting 3 hours after linezolid administration and lasted for 3 hours has removed 30% of linezolid from the body. No data is available for the removal of linezolid by peritoneal dialysis or hemoperfusion.

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.

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 a new class of antimicrobials, the oxazolidinones and is clinically active against aerobic Gram positive bacteria. In vitro activity of linezolid also includes some anaerobic bacteria. Linezolid selectively inhibits bacterial protein synthesis by a unique mechanism of action; therefore no cross resistance is expected of linezolid with other classes of antibiotics. 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.

Susceptibility:

Results of the studies of time/killing curve, has shown that linezolid has bacteriostatic effect on enterococci and staphylococci. Linezolid is found to have bactericidal effect on most of the strains of streptococci. Linezolid has shown both in vitro and clinical activity against below mentioned microorganisms:

Susceptible Aerobic Gram-positive Bacteria:

*Enterococcus faecium**

Enterococcus faecalis

*Staphylococcus aureus**

Coagulase negative Staphylococci

*Streptococcus agalactiae**

*Streptococcus pneumoniae**

*Streptococcus pyogenes**

Group C Streptococci

Group G Streptococci

Susceptible Anerobic Gram Positive Bacteria:

Clostridium perfringens

Peptostreptococcus anaerobius

Peptostreptococcus strains

Resistant Bacteria:

Haemophilus influenzae

Moraxella catarrhalis

Neisseria suşları

Enterobactericeae

Pseudomonas strains

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

5.2. Pharmacokinetic properties

Absorption

Linezolid is rapidly and extensively absorbed following oral administration. Maximum plasma concentrations are reached within 1-2 hours of dosing and absolute bioavailability of linezolid is approximately 100%. Therefore, linezolid can be administered oral or intravenously without dose adjustments.

Linezolid can be administered regardless of the time of the food intake. When high fat food is administered with linezolid, time to reach the maximum plasma concentration increases from 1.5

hours to 2.2 hours and C_{max} decreases approximately 17%. However total exposure criteria, $EAA_{0-(\infty)}$ is similar for both cases.

Distribution

Human and animal studies have shown that linezolid is distributed easily in highly-perfused tissues. Plasma protein binding of linezolid is about 31% and is not concentration dependent. Volume of distribution at steady-state averages at about 40-50 liters in healthy adults.

Biotransformation

Linezolid is primarily metabolized by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives; aminoethoxyacetic acid metabolite (A) and hydroxyethyl glycine metabolite (B).

Elimination

Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. In steady-state conditions, each dose is excreted approximately 30% as linezolid, 40% as B metabolite and 10% as A metabolite in the urine. Renal clearance of linezolid is low (approximately 40 ml/min) and associated with net tubular reabsorption. No linezolid is found in the feces whilst approximately 6% and 3% of each dose appears as metabolite A and metabolite B, respectively.

Linearity/non-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.

Pharmacokinetic parameters of linezolid following single or multiple oral and intravenous doses is summarized in the table below:

Mean Pharmacokinetic Parameters of Linezolid in Adults (Standard deviation)						
Linezolid doses	**C_{max} µg/ml**	**C_{min} µg/ml**	**T_{max} hour**	**EAA* µg*h/ml**	**$t_{1/2}$ hour**	**CL ml/min**
600 mg tablet						
Single dose	12.70 (3.96)	---	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
Twice daily	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg IV infusion solution‡						
Single dose	12.90 (1.60)	---	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
Twice daily	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)
600 mg oral suspension						
Single dose	11.00 (2.76)	---	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)
*For single dose EAA=$EAA_{0-\infty}$; for multiple dose = $EAA_{0-[tgr]}$						
‡ Data dose is normalized according to 625 mg, IV dose is administered as infusion for 0.5 hour						
C_{max}= Maximum plasma concentration; C_{min}=Minimum plasma concentration; T_{max}= Time to reach C_{max}; EAA=Area under concentration-time curve; $t_{1/2}$= Elimination half-life; CL= Systemic clearance						

Special populations

Geriatric patients:

The pharmacokinetics of linezolid is not significantly altered in elderly patients aged 65 and over. Therefore no dose adjustment is required for elderly patients.

Pediatric patients:

The pharmacokinetics of linezolid in pediatric patients aged 0-17 (including preterm newborns) is studied in healthy adolescents aged 12-17 and in children aged 1 week to 12 years old by single dose IV studies.

C_{max} and volume of distribution of linezolid is independent of age in pediatric patients. However, the clearance of linezolid differs depending the age. Except for preterm newborns younger than 1 week, the clearance of linezolid is fastest in 1 week-11 years old age group, therefore single dose EAA

values are higher and half-life is lower compared to adults. Linezolid clearance decreases gradually with increasing age in pediatric patients and in adolescents mean clearance values are similar to those of adults. The difference in linezolid clearance and EAA values are greater in pediatric age groups compared to adults.

Similar daily EAA values were observed in pediatric patients aged 0-11 who received every 8 hours daily linezolid and adults and adolescents who received every 12 hours daily linezolid, approximately.

Gender:
No adjustment is required regarding the gender.

Patients with renal insufficiency:
Pharmacokinetics of the parent drug, linezolid does not change in renal insufficiency, however two primary metabolites of linezolid may accumulate in renal insufficiency and the accumulation level may increase with the severity of renal insufficiency. Clinical significance of accumulation of these two metabolites is not known in patients with severe renal insufficiency. As similar plasma concentrations have been reached regardless of the kidney function, no dose adjustment is required in patients with renal insufficiency. However, since there is not data available regarding the accumulation of the primary metabolites, risk potential of accumulation should be considered. Both linezolid and the two metabolites are eliminated by dialysis. There is no data available regarding the effect of peritoneal dialysis on pharmacokinetics of linezolid. During the dialysis starting 3 hours after linezolid administration and lasted for 3 hours, 30% of the linezolid dose is removed from the body; therefore linezolid should be administered after hemodialysis.

Patients with hepatic insufficiency:
The pharmacokinetics of linezolid is not altered in patients with mild to moderate hepatic insufficiency (Child-Pugh Class A or B) (n=7). According to available data, no dose adjustment is recommended in patients with mild to moderate hepatic insufficiency. Pharmacokinetics of linezolid in patients with severe hepatic insufficiency has not been evaluated.

5.3. Preclinical safety data

Although no life-long studies were performed in animals to determine the carcinogenic potential of linezolid, no mutagenic or clastogenic potential was observed with linezolid in various tests such as Ames and AS52 analyses, in vitro unscheduled DNA synthesis (UDS) tests, in vitro chromosomal aberration tests on human lymphocytes and in vivo micronucleus tests on mice.

Fertility or reproductive performance of mature female rats were not affected by linezolid; fertility and reproductive performance of mature male rats were decreased reversibly at ≥50 mg/kg/daily doses, at the exposure levels approximately equal or higher to those expected in humans based on EAA. Epithelial cell hypertrophy in epididymis may contribute to decreased fertility by affecting sperm maturation.

Similar epididymal changes were not observed in dogs. Although sperm concentrations in testis were in normal levels, their concentration at cauda epididymis and motility of sperms in vas deferens has been decreased. A slight decrease in fertility was observed in juvenile male rats treated with linezolid (at 50 mg/kg/daily doses from 7-36 days and at 100 mg/kg/daily doses from 37-55 days, exposure levels 0.4 to 1.2 fold of those expected in humans based on AUC's) for nearly the entire period of sexual maturation. No histopathological change has been observed suggesting adverse effects in male reproductive system.

Teratogenic/non-teratogenic effects and lactation: See Section 4.6. Pregnancy and lactation.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Sodium citrate
Citric acid anhydrous
Glucose monohydrate
Sodium chloride
Sodium hydroxide
Water for injection

6.2. Incompatibilities

Following drugs were found to be physically incompatible with LINEDOR IV solution for infusion, administered with a Y line: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and sulphamethoxazole/trimethoprim. Additionally LINEDOR IV solution for infusion is chemically incompatible with ceftriaxone sodium.

If the same intravenous line is to be used for sequential infusion of several drugs, then the line should be flushed prior to and following the administration of LINEDOR IV solution for infusion with a compatible infusion solution.

LINEDOR IV solution for infusion is compatible with the following solutions:
5% dextrose injection
0.9 sodium chloride injection
Ringer lactate injection

6.3. Shelf-life

36 months

6.4. Special precautions for storage

Store at room temperature not exceeding 25 ºC. Do not freeze. LINEDOR IV solution of infusion may acquire a yellow color with time; however its potency is not affected unfavorably.
Vials should be used immediately after opening. Unused solutions should be discarded.

6.5. Nature and contents of container

300 ml colorless, Type I glass vial overwrapped with bromobutyl stopper sealed with a whitish (transparent) flip-off cap and a box containing patient information leaflet.

6.6. Special precautions for disposal and other handling

Unused products or waste substances must be destroyed in accordance with “Medical Waste Control Regulation” and “Packaging and Packaging Waste Control Regulations”.

Parenteral medicinal products should be visually inspected for particles prior to use and only clear solutions, without particles should be used. Any unused solutions should be discarded.

LINEDOR solution for infusion should be administered as intravenous infusion over a period of 30-120 minutes.

Additives should not be introduced into this solution. If linezolid is to be given concomitantly with other drugs, each drug should be given separately in accordance with its own directions for use.

7. MARKETING AUTHORIZATION HOLDER

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9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 10.11.2014

10. DATE OF REVISION OF THE TEXT