SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

POLİNOKSİD 2 mg/ml Solution for I.V. Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains:

Active Substance:
Linezolid 2 mg/ml

Excipients:

Dextrose anhydrous (glucose)	45,67 mg/ml
Sodium citrate dihydrate	1,64 mg/ml
Sodium hydroxide	q.s for pH 4.8

"For a full list of excipients, see section 6.1."

3. PHARMACEUTICAL FORM

Solution for IV infusion.
Clear, homogeneous solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

POLİNOKSİD preparations are indicated for the treatment of the following infections caused by susceptible strains of the following microorganisms. POLİNOKSİD has no clinical efficacy against Gram negative pathogens and is not indicated in the treatment of Gram negative infections. Specific antibacterial therapy against Gram-negative organisms must be initiated concomitantly if a Gram-negative pathogen is documented or suspected.

- **Vancomycin-resistant *Enterococcus faecium* infections:** Including cases with accompanying bacteremia.
- **Nosocomial pneumonia:** Caused by *Staphylococcus aureus* (methicillin susceptible and resistant strains) or *Streptococcus pneumoniae* (including multidrug resistant strains [MDRSP]).
- **Complicated infections of skin and skin structures (including diabetic foot infections, not accompanied with osteomyelitis):** Caused by *Staphylococcus aureus* (methicillin susceptible and resistant strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*.

POLİNOKSİD is indicated 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. POLİNOKSİD is not active against infections caused by Gram-negative pathogens. POLİNOKSİD 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. POLİNOKSİD has not been studied in patients with decubitus ulcer.

- **Uncomplicated infections of skin and skin structures:** Caused by Staphylococcus aureus (only methicillin-sensitive strains) or Streptococcus pyogenes.
- **Community-acquired pneumonia:** Caused by Streptococcus pneumoniae (including multi-drug resistant strains [MDRSP]) or Staphylococcus aureus (only methicillin-sensitive strains), including cases with accompanying bacteremia.

MDRSP refers to strains resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline and trimethoprim / sulfamethoxazole.

4.2. Posology and method of administration

Posology / frequency and duration of administration
Adults:
Dose recommendation for POLİNOKSİD formulations for the treatment of infections are given in the following table. POLİNOKSİD doses are administered every 12 hours. Adult patients with methicillin-resistant Staphylococcus aureus infection should be treated with linezolid 600 mg every 12 hours.

Dosage scheme for POLİNOKSİD			
	Dosage, route of administration and frequency		**Recommended duration of treatment**
Infection*	**Pediatric patients (0-11 years old)****	**Adolescents and Adults (12 and over)**	
Vancomycin-resistant Enterococcus faecium infections, including cases with accompanying bacteremia	10 mg/kg IV or oral every 8 hours†	600 mg IV or oral every 12 hours†	14-28 days
Nosocomial pneumonia	10 mg/kg IV or oral every 8 hours†	600 mg IV or oral every 12 hours†	10-14 days
Complicated infections of skin and skin structures			
Community acquired pneumonia			

including cases with accompanying bacteremia			
Uncomplicated infections of skin and skin structures	<5 years of age: 10 mg/kg IV or oral every 8 hours† 5 - 11 years of age: 10 mg/kg IV or oral every 12 hours†	In adults: 400 mg oral every 12 hours† In adolescents: 600 mg oral every 12 hours†	10-14 days
* Caused by specified pathogens (See Section 4.1 Therapeutic indications)			
† Oral use with linezolid film coated tablets or linezolid granules for oral suspension			
** Treatment should be initiated at 10 mg/kg every 12 hours in premature newborns younger than 7 days (gestational week <34 weeks). Dose escalation to 10 mg / kg every 8 hours should be considered in case of poor clinical response. In all newborns, the dose should be 10 mg / kg every 8 hours from day 7 of birth.			

In controlled clinical trials, the time defined in the treatment protocol for all infections is 7 to 28 days. The duration of treatment is determined by the treating physician dependent on the pathogen, the site of infection and its severity, and on the patient's clinical response.

Dosage adjustment is not necessary when intravenous administration is followed by oral administration. Patients who started treatment with POLİNOKSİD I.V. solution for infusion may be converted to linezolid tablets or granules for oral suspension depending on the clinician's discretion when required clinically.

Method of administration:
For intravenous administration.
POLİNOKSİD IV Solution for Infusion should be administered intravenously over a period of 30 to 120 minutes.

Additional information on special populations:
Renal failure:
No dose adjustment is required (See Sections 5.2 Pharmacokinetic properties and 4.4 Special warnings and precautions for use).

Severe renal failure (creatinine clearance < 30 ml/min): No dose adjustment is required. In patients with severe renal insufficiency, although of unknown clinical significance, due to higher exposure (up to 10 fold) to the two primary metabolites of POLİNOKSİD, POLİNOKSİD should be used with special caution in these patients only when the anticipated benefit is considered to outweigh the theoretical risk.

As approximately 30% of a POLİNOKSİD dose is removed during the first 3 hours of hemodialysis, POLİNOKSİD should be given after dialysis in patients receiving such treatment.

The primary metabolites of POLİNOKSİD are removed to some extent by hemodialysis, 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.

Therefore, POLİNOKSİD should be used with 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 POLİNOKSİD administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure.

Hepatic failure:
No dose adjustment is required. However, there are limited clinical data and it is recommended that POLİNOKSİD should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk (See sections 5.2.Farmakokinetik properties; 4.4 Special warnings and precautions for use).

Pediatric population:
POLİNOKSİD dose is determined by age and body weight in pediatric patients (see section 4.2 Posology / frequency and time of administration, dosage scheme for POLİNOKSİD)

Geriatric population:
No dose adjustment is required. (See sections 5.2.Farmakokinetik properties; 4.4 Special warnings and precautions for use)

Other:
No dose adjustment is required based on gender.

4.3. Contraindications
POLİNOKSİD formulations are contraindicated in patients who are hypersensitive to linezolid or to any of the ingredients.

Monoamine Oxidase Inhibitors:
POLİNOKSİD 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

If the patient is not monitored for blood pressure, POLİNOKSİD should not be used in patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis, and / or patients who use the following medications: directly or indirectly acting sympathomimetic agents (e.g., adrenergic bronchodilators, pseudoephedrine, phenylpropanolamine), vasopressor agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine) (See Section 4.5 Interaction with other medicinal products and other forms of interaction).

Potential Serotonergic Interactions:

The use of POLİNOKSİD in patients who use drugs acting on the serotonin system may cause serotonin syndrome. Therefore use of linezolid should be avoided in patients who take serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5HT-1 receptor agonists (tryptans), meperidine or buspirone, directly or indirectly acting sympathomimetic agents (Including adrenergic bronchodilators, pseudoephedrine, and phenylpropanolamine), vasopressor agents (such as epinephrine, norepinephrine); dopaminergic agents (dopamine, dobutamine) and pethidine (see 4.5 Interactions with other medicinal products and other forms of interaction); in those with carcinoid syndrome or in cases where the signs and symptoms of serotonin syndrome cannot be monitored closely.

In patients who use drugs acting on the serotonin system treatment with POLİNOKSİD should be initiated in the presence of a life-threatening infection and discontinuation of the drug should be evaluated by the treating specialist.

POLİNOKSİD should not be used in patients with bipolar depression, schizoaffective disorder and acute confusional state.

Animal data suggest that linezolid and its metabolites may pass into breast milk. Therefore, breastfeeding should be discontinued prior to and throughout administration.

4.4. Special warnings and precautions for use

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In follow-up cases, 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. Complete blood count should be monitored weekly in patients receiving POLİNOKSİD, particularly in those who use for more than two weeks, in those with prior myelosuppression, in those who use other drugs associated with myelosuppression and in those who received prior or concomitant antibiotic therapy for chronic infection. Discontinuation of POLİNOKSİD therapy should be considered in patients who develop myelosuppression or with increased severity.

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. 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.

In compassionate use studies, a higher incidence of serious anaemia was reported in patients receiving linezolid for more than the maximum recommended duration of 28 days. These patients more often required blood transfusion. Cases of anaemia requiring blood transfusion have also been reported post marketing, with more cases occurring in patients who received linezolid therapy for more than 28 days.

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.
<u>Mortality imbalance in patients with a catheter-related Gram positive bloodstream infection in a clinical study</u>
Excess mortality was seen in patients treated with linezolid, compared to vancomycin / dicloxacillin / oxacillin, in an open-label study in seriously ill patients with intravascular catheter-related infections [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 purely by Gram-positive organisms (odds ratio 0.96; 95% confidence interval: 0.58-1.59) but were significantly higher (p=0.0162) in the linezolid arm in patients 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 within 7 days following discontinuation of the drug. More patients in the linezolid arm acquired Gram-negative pathogens during the study and died from infection caused by Gram-negative pathogens and polymicrobial infections. Therefore, in complicated skin and soft tissue infections POLİNOKSİD should only be used in patients with known or possible co-infection with Gram-negative organisms if there are no alternative treatment options available (See Section 4.1 Therapeutic indications). In these circumstances treatment against Gram-negative organisms must be initiated concomitantly.

POLİNOKSİD has no clinical efficacy against Gram negative pathogens and is not indicated in the treatment of Gram negative infections. Specific antibacterial therapy against Gram-negative organisms must be initiated concomitantly if a Gram-negative pathogen is documented or suspected (See Section 4.1 Therapeutic indications).

Pseudomembranous colitis that may range in severity from mild to life-threatening has been reported with nearly all antibacterial agents (including linezolid). Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agent.

Clostridium difficile-associated diarrhea (CDAD) has been reported in association with the use of nearly all antibiotics including linezolid and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal fluorescence of the colon, leading to overproduction of *C. difficile*.

Antibiotic Associated Diarrhea and Colitis
C. difficile produces A and B toxins that cause CDAD. Excessive toxin producing strains of *C. difficile* cause increased morbidity and mortality; these infections may be refarctory to antimicrobial therapy and patients may need colectomy. The possibility of CDAD should be considered in all patients with diarrhea following antibiotic use. Medical history should be considered because CDAD has been reported to have emerged 2 months after the administration of antibacterial agents.

If antibiotic-associated diarrhea or antibiotic-associated colitis is suspected or confirmed, antibiotic treatment should be discontinued.

Once CDAD is diagnosed, appropriate treatment modalities should be initiated. Mild cases of CDAD usually only respond to drug discontinuation. Treatment with fluid and electrolyte treatment, protein supplements and a clinically effective antibacterial agent against Clostridium difficile should be considered in mild to severe cases.

Mitochondrial dysfunction
Post marketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid (a reversible, non-selective MAO inhibitor). Some MAO inhibitors have been associated with hypoglycaemic episodes in diabetic patients using insulin or hypoglycaemic agents. While a causal relationship between linezolid and hypoglycemia has not been established, diabetic patients should be cautioned of potential hypoglycemic reactions when treated with linezolid.

If hypoglycemia occurs, a decrease in the dose of insulin or oral hypoglycemic agent, or discontinuation of oral hypoglycemic agent, insulin, or linezolid may be required.

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.

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 the maximum recommended duration of 28 days. In the case of optic neuropathy causing visual loss, patients were treated with periods longer than the maximum recommended duration of treatment. Peripheral and optic neuropathy have been reported primarily in patients treated with linezolid for longer than 28 days.

In cases where peripheral or optic neuropathy develops, it should be decided whether to continue using linezolid considering potential risks.

If symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect occurs, prompt evaluation is recommended with referral to an ophthalmologist as necessary. In case of prolonged treatment (3 months or more) with POLİNOKSİD, visual function should be regularly monitored in all patients who report new symptoms of impairment, regardless of the duration of POLİNOKSİD treatment.

There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis.

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

Convulsions
Convulsions have been reported in patients treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported. Patients should be advised to inform their physician if they have a history of seizures.

Monoamine oxidase inhibutors
Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI); however, at the doses used for antibacterial therapy, it does not exert an antidepressive effect. There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use

in these circumstances unless close observation and monitoring of the recipient is possible (see section 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction).

Serotonin syndrome
Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of linezolid and serotonergic agents is therefore contraindicated except where it is essential.

In cases where co-administration of POLİNOKSİD and serotonergic agents is clinically appropriate, 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 physicians should consider discontinuing either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur.
Concomitant use of linezolid with rifampicin in healthy volunteers decreased the linezolid C_{max} and AUC by 21% and 32% respectively. The mechanism of this interaction and its clinical significance are unknown.

Tyramine-rich foods
Patients should be advised to avoid 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. POLİNOKSİD should not be used in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism. (See section 4.3).

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).

Fertility impairment
Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans; possible effects

of linezolid on the human male reproductive system are not known (see section 5.3 Preclinical safety data).

Clinical trials
The safety and effectiveness 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 ischemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

Each ml of solution also contains 5 mmole of sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

Each ml of the solution contains 45.67 mg of glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance.

4.5. Interaction with other medicinal products and other forms of interaction
In normotensive healthy volunteers, POLİNOKSİD 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. Initial doses of agents with a vasopressive effect, including dopaminergic agents, should be kept low and should be carefully titrated to achieve the desired response.

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, 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. This 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, while co-administration is contraindicated (see section 4.3 Contraindications), management of patients for whom treatment with linezolid and

serotonergic agents is essential, is described in section 4.4 Special warnings and precautions for use.

Drugs metabolized by cytochrome P450
POLİNOKSİD is not detectably metabolized 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). Therefore, no CYP450-induced drug interactions are expected with POLİNOKSİD. Simultaneous administration of POLİNOKSİD does not significantly alter the pharmacokinetic properties of S-warfarin, which is extensively metabolised by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, can be used together with POLİNOKSİD without changing the dosage regimen.

Antibiotics

Rifampicin: The effect of rifampicin on the pharmacokinetics of linezolid was studied in 16 healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the 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.

Aztreonam
The pharmacokinetics of POLİNOKSİD or aztreonam is not altered when administered together.

Gentamicin
The pharmacokinetics of POLİNOKSİD or gentamicin is not altered when administered together.

Monoamine Oxidase Inhibition
POLİNOKSİD is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, it has the potential for interaction with adrenergic and serotonergic agents. There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible

Adrenergic Agents
Some individuals receiving POLİNOKSİD may experience a reversible enhancement of the response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Initial doses of adrenergic agents, such as dopamine or adrenaline, should be reduced and titrated to achieve the desired response.

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).

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.

Concomitant use of linezolid with tramadol may increase the risk of seizure.
Concomitant use with other myelosuppressive drugs may increase the risk of developing myolosuppression.

Drug-laboratory test interactions
There are no drug-laboratory test interactions reported so far.

Additional information on special populations
Renal / Hepatic failure:
No interaction study has been detected.

Pediatric population:
No interaction study has been detected.

4.6. Pregnancy and lactation
General recommendation
Pregnancy category: C

Women with childbearing potential / Contraception
An effective contraceptive method should be used during treatment.

Pregnancy
There are no adequate and well-controlled studies in pregnant women.
Studies in animals showed evidence of reproductive toxicity (see section 5.3). POLİNOKSİD should not be used during pregnancy only if the potential benefit outweighs the theoretical risk. A potential risk for humans exists.

Lactation
Studies in animals have shown excretion of linezolid and its metabolites in breast-milk. Therefore, breastfeeding should be discontinued prior to and throughout administration.

Reproductive ability/Fertility

In animal studies, linezolid caused a reduction in fertility (See section 5.3). .

4.7. Effects on ability to drive and use machines

Effects of POLİNOKSİD on ability to drive and use machines have not been evaluated. Patients using POLİNOKSİD should be warned about the potential for dizziness or symptoms of visual impairment and should be advised not to drive or operate machinery if any of dizziness occurs.

4.8. Undesirable effects

Adverse reactions listed in the table below with their frequency are based on causality data obtained in clinical studies that enrolled more than 2000 adult patients who received the recommended linezolid doses for up to 28 days. It is based on clinical trial data obtained when using POLİNOKSİD doses.

Those most commonly reported were diarrhea (8.4 %), headache (6.5%), nausea (6.3%) and vomiting (4.0%).

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.
Undesirable effects are listed according to the following categories:

Very common (≥ 1/10); 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)

Infections and Infestations

Common: Candidiasis (primarily oral candidiasis and vaginal candidiasis) and fungal infections
Uncommon: Vaginitis
Rare: Antibiotic-associated colitis (including pseudomembranous colitis)*

Blood and lymphatic system disorders

Common: Anemia*†
Uncommon: Eosinophilia, leukopenia *, neutropenia, thrombocytopenia *
Rare: Pancytopenia *
Unknown: Myelosuppression *, sideroblastic anemia *

Immune system disorders

Unknown: Anaphylaxis

Metabolism and nutrition disorders

Uncommon: Hyponatremia
Unknown: Lactic acidosis*

Psychiatric disorders

Uncommon: Insomnia

Nervous system disorders

Common: Headache, taste perversion (metallic taste), dizziness
Uncommon: Convulsions*, hypoaesthesia, paraesthesia
Unknown: Serotonin syndrome**, peripheral neuropathy*

Eye disorders

Uncommon: Blurred vision*
Rare: Changes in visual field defect*
Unknown: Optic neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in color vision*

Ear and Labyrinth Disorders

Uncommon: Tinnitus

Cardiac disorders

Uncommon: Arrhythmia (tachycardia)

Vascular disorders

Common: Hypertension
Uncommon: Transient ischaemic attacks, phlebitis, thrombophlebitis

Gastrointestinal disorders

Common: Diarrhoea, nausea, vomiting, localisated or general abdominal pain, constipation, dyspepsia
Uncommon: Pancreatitis, gastritis, abdominal distension, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder
Rare: Superficial tooth discolouration

Hepatobiliary Disorders

Common: Abnormal liver function test; increased AST, ALT or alkaline Phosphatase
Uncommon: Increased total bilirubin

Skin and subcutaneous tissue disorders

Common: Rash, pruritus
Uncommon: Dermatitis, diaphoresis, urticaria
Unknown: Bullous disorders such as those described as Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, alopecia

Renal and urinary disorders

Common: Increased BUN
Uncommon: Renal failure, increased creatinine, polyuria

Reproductive system and breast disorders
Uncommon: Vulvovaginal disorder

General Disorders and Administration Site Conditions
Common: Fever, localized pain
Uncommon: Chills, fatigue, 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.

Haematology
Common: Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.
Uncommon: Increased reticulocyte count. Decreased neutrophils.
* See section 4.4
** See section 4.3 and 4.5
† In controlled clinical trials where linezolid was administered for up to 28 days, 1.0% 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 or longer was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for less than 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 or longer and 15% (8/53) in those treated for less than 28 days.

The following adverse reactions to POLİNOKSİD were considered to be serious in isolated cases: localized abdominal pain, transient ischaemic attacks and hypertension.

Additional information on special populations
Pediatric Population
Safety data from clinical studies based on more than 500 pediatric patients (from birth to 17 years) do not indicate that the safety profile of linezolid for pediatric patients differs from that for adult patients.

4.9. Overdose and therapy

No specific antidote is known.

In case of overdose, supportive care is advised together with maintenance of glomerular filtration.

Hemodialysis can facilitate rapid elimination of linezolid. In a Phase 1 clinical study, approximately 30% of a linezolid dose is removed at the end of 3 hours of haemodialysis initiated 3 hours following the administration of linezolid. 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.

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 antibacterial
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 useful in the treatment of aerobic gram-positive bacterial infections. The in vitro activity spectrum of linezolid also includes some anaerobic bacteria. Linezolid inhibits bacterial protein synthesis by a mechanism of action different from other antibacterial agents; therefore cross resistance between linezolid and antibiotics from other classes is not expected. Linezolid binds to 23S of the 50S subunit on the bacterial ribosome and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

The post-antibiotic effect (PAE) of linezolid for *Staphylococcus aureus* is approximately 2 hours. When measured in animal models, the *in vivo* PAE was 3.6 and 3.9 hours for *Staphylococcus aureus* and *Streptococcus pneumoniae*, respectively. In animal studies, the key pharmacodynamics parameter for efficacy was the time for which the linezolid plasma level exceeded the minimum inhibitory concentration (MIC) for the infecting organism.

Susceptibility

The results of time/kill curve studies have shown that linezolid is bacteriostatically effective against enterococci and staphylococci. Linezolid is found to be effective against streptococci in the majority of strains.
Linezolid was found to be effective in both the in vitro conditions and clinical infections against the majority of the following 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 Anaerobic Gram-positive Bacteria:
Clostridium perfringens
Peptostreptococcus anaerobius
Peptostreptococcus suşları

Resistant Bacteria
Haemophilus influenzae
Moraxella catarrhalis
Neisseria species
Enterobactericeae
Pseudomonas species
* Clinical efficacy has been demonstrated for these isolates in approved clinical indications
Whereas linezolid shows some in vitro activity against *Legionella, Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, there are insufficient data to demonstrate clinical efficacy.

Resistance
Cross 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.

Resistance to linezolid is associated with point mutations in the 23S rRNA.

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 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.

Clinical trials on pediatric population

In an open study, the efficacy of linezolid (10 mg/kg q8h) was compared to vancomycin (10-15 mg/kg q6-24h) 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. Clinical cure rates in the clinically evaluable population were 89.3% (134/150) and 84.5% (60/71) for linezolid and vancomycin, respectively (95%CI: -4.9, 14.6)

5.2. Pharmacokinetic Properties

General properties:

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

Absorption

Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 1-2 hours of dosing and absolute bioavailability is approximately 100%. For this reason, linezolid can be administered orally or intravenously without the need for dose adjustment. Absorption is not significantly affected by food. Absorption from the oral suspension is similar to that achieved with the film tablets.

Plasma linezolid C_{max} and C_{min} (mean and [SD]) at steady-state following twice daily intravenous dosing of 600 mg have been determined to be 15.1 [2.5] mg/l and 3.68 [2.68] mg/l, respectively.

In another study following oral dosing of 600 mg twice daily to steady-state, C_{max} and C_{min} were determined to be 21.2 [5.8] mg/l and 6.15 [2.94] mg/l, respectively. Steady-state conditions are achieved by the second day of dosing.

Linezolid can be administered regardless of the time of meal when a high fat meal is administered with Linezolid, the time to reach the maximum plasma concentration is from 1.5 hours to 2.2 hours and the C_{max} is reduced by about 17%. However, $AUC_{0-(\infty)}$, which is the total exposure criterion is similar in both cases.

Distribution

Volume of distribution at steady-state averages at about 40-50 litres in healthy adults. 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.

Human and animal pharmacokinetic studies show that linezolidin is easily dispersed in well-perfused tissues.

Biotransformation

Linezolid is primarily metabolized 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 characterized.

Elimination

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 nonrenal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.

Linezolid is primarily excreted under steady-state conditions in the urine as PNU-142586 by 40%, and PNU-142300 metabolite by 10%. Renal clearance of linezolid is low (mean 40 mL / min) and suggests clear tubular reabsorption. Virtually no parent drug is found in the faeces whilst approximately 6% and 3% of each dose appears as PNU-142586 metabolite and PNU-142300 metabolite, respectively. The elimination half-life of linezolid averages at about 5-7 hours.

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 nonrenal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.
The average pharmacokinetic parameters after single or multiple oral and intravenous doses of linezolidine are 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**	**AUC* 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)
Every 12	21.20	6.15	1.03	138.00	5.40	80

hours	(5.78)	(2.94)	(0.62)	(42.10)	(2.06)	(29)
600 mg Solution for IV Infusion ‡						
Single dose	12.90 (1.60)	--	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
Every 12 hours	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)
* AUC = $AUC_{0-(\infty)}$ for single dose; = $AUC_{0-[tgr]}$ for multiple dose						
‡ The data were normalized to 625 mg dose, IV dose was given with a 0.5 hour infusion.						
C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; T_{max} = The time to reach Cmax; AUC = area under the concentration time curve; t½ = elimination half-life; CL = systemic clearance						

Special Populations

Geriatric patients:

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

Pediatric patients:

There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old). Therefore, its use in this age group is not recommended. Further studies are needed to establish safe and effective dosage recommendations. Pharmacokinetic studies indicate that after single and multiple doses in children (one week to 12 years), linezolid clearance (based on kg body weight) was greater in pediatric patients than in adults. But it decreases with increasing age.

In children one 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 neonates up to one week of age, the systemic clearance of linezolid (based on kg body weight) increases rapidly in the first week of life. Therefore, neonates given 10 mg/kg every 8 hours daily will have the greatest systemic exposure on the first day after delivery. However, excessive accumulation is not expected with this dosage regimen during the first week of life as clearance increases rapidly over that period.

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

In pediatric 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 pediatric patients with central nervous system infections is not recommended.

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.

Renal failure:
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 (creatinine clearance < 30 ml/min). However, there was no increase in AUC of parent drug. Although there is some removal of the major metabolites of linezolid by haemodialysis, metabolite plasma levels after single 600 mg doses were still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

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

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

Hepatic failure:
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) (n=7). The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e. Child-Pugh class C) have not been evaluated. However, as linezolid is metabolized by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Based on available data, no dose adjustment is recommended in patients with mild to moderate hepatic impairment.

5.3. Preclinical safety data

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those expected 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 one 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 four times or equivalent, respectively, to those expected 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 expected 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 fetal 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 myelosupression in rats and dogs.

In rats administered linezolid orally for six months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in one male at this dose level at a three 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 in the standard battery of studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium Citrate Dihydrate
Citric acid anhydrous
Dextrose anhydrous (glucose)
Sodium hydroxide
Hydrochloric acid
Water for injection

6.2. Incompatibilities

Physical incompatibilities were determined with especially the following drugs when given in combination with POLİNOKSİD solution for I.V. infusion: Amphotericin B, chlorpromazine HCl, Diazepam, Pentamidine isethionate, Erythromycin lactobionate, Phenytoin sodium and Trimethoprim sulphamethoxazole. Additionally, POLİNOKSİD solution for IV infusion is chemically incompatible when combined with ceftriaxone sodium.

The same intravenous line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following administration of POLİNOKSİD solution for IV infusion with an infusion solution compatible with POLİNOKSİD.

POLİNOKSİD solution for IV infusion is known to be compatible with following solutions:

- 5% Dextrose injection
- 0.9% sodium chloride injection
- Ringer lactate injection

6.3. Shelf-life

24 months

6.4. Special precautions for storage

Store the bags in the foil packaging until ready to use.
The bags should be used immediately after opening. Any unused solution must be discarded
Store at room temperature below 25ºC. Do not freeze. POLİNOKSİD Solution for IV infusion may turn into yellow over time, but the potency is not adversely affected.

6.5. Nature and contents of container

Ready to use transparent plastic bag with one opening, 300 ml

6.6. Special precautions for disposal and other handling

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging and Packaging Waste Control Regulation".

POLİNOKSİD solution for IV infusion is in disposable, ready to use infusion bags. Parenteral drug products should be visually inspected prior to use and for the presence of particles. The presence of minor leaks must be checked by squeezing the bag firmly. If any leak is detected, solution should not be used as sterility may be impaired.

Keep the infusion bags in the packaging until it is ready to use (See Storage conditions). POLİNOKSİD Solution for IV Infusion should be administered intravenously over a period of 30 to 120 minutes.

Do not use the intravenous infusion bags in series connections (See “Incompatibilities”).
Do not add additives in the intravenous solution. If linezolid is to be given concomitantly with other drugs, each drug should be given separately in accordance with its own route of administration.

7. MARKETING AUTHORISATION HOLDER
POLİFARMA İLAÇ SAN. VE TİC. A.Ş.
Vakıflar OSB Mahallesi,
Sanayi Caddesi, No:22/1
Ergene/Tekirdağ/TURKEY
+90 282 675 14 04
+90 282 675 14 05

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