SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

LINEZAN 2 mg/ml Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml contains 2 mg linezolid.

300 ml infusion bags contain 600 mg linezolid.

Excipients with known effect:
Each 300 ml also contains 114 mg sodium and 13.7 g glucose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

LINEZAN 2 mg/ml solution for infusion is presented in a single use bag containing a clear, colorless to sub yellow solution, free from visible particles.

The pH is between 4.6 and 5.0 and osmolality is between 285 and 310 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Linezolid is indicated for the treatment of adults and adolescents (12 years and older) and pediatric patients (birth through 11 years of age) with the following infections caused by susceptible strains of Gram-positive bacteria only. Linezolid is not indicated for the treatment of Gram-negative infections. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected (see sections 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

Community-acquired pneumonia caused by *Streptococcus pneumoniae* (penicillin-sensitive strains only), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-sensitive strains only).

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant strains) or *Streptococcus pneumoniae* (penicillin-sensitive strains only).

Complicated skin and soft tissue infections, caused by *Staphylococcus aureus* (methicillin-sensitive and methicillin-resistant strains), *Streptococcus pyogenes* or *Streptococcus agalactiae*.

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

Linezolid should not be initiated as a first line therapy for community acquired pneumonia but may be

considered if resistant strains are suspected or proven or in presence of drug allergy.

4.2 Posology and method of administration

Patients whose therapy is started with linezolid injection may be switched to linezolid tablets or linezolid for oral suspension, with no dosage adjustment.

Linezolid oral dosage forms are unavailable in this brand but are available in other brands. Where oral administration is required, refer to the specific product information of these brands for the relevant dosage and administration instructions.

<table>
<tr><th colspan="3">Dosing Recommendations for Adults and Adolescents (12 years old and older)</th></tr>
<tr><th>Indications</th><th>Dosage and Route of Administration</th><th>Recommended Duration of Treatment (Consecutive days)</th></tr>
<tr><td>Nosocomial pneumonia</td><td rowspan="3">600 mg IV every 12 hours</td><td rowspan="3">10-14 days</td></tr>
<tr><td>Community acquired pneumonia</td></tr>
<tr><td>Complicated skin and soft tissue infections</td></tr>
<tr><td>Vancomycin-resistant Enterococcus infections</td><td>600 mg IV every 12 hours</td><td>14 – 28 days</td></tr>
<tr><th colspan="3">Dosing Recommendations for Pediatric Patients (Birth* through 11 years of age)</th></tr>
<tr><th>Indications</th><th>Dosage and Route of Administration</th><th>Recommended Duration of Treatment (Consecutive days)</th></tr>
<tr><td>Nosocomial pneumonia</td><td rowspan="3">10 mg/kg IV every 8 hours</td><td rowspan="3">10-14 days</td></tr>
<tr><td>Community acquired pneumonia</td></tr>
<tr><td>Complicated skin and soft tissue infections</td><td>10 mg/kg IV every 8 hours</td></tr>
<tr><td>Vancomycin-resistant Enterococcus infections</td><td>10 mg/kg IV every 8 hours</td><td>14 – 28 days</td></tr>
<tr><td colspan="3">Duration of treatment is variable, depending on the pathogen isolated, site of infection and its severity. To date the maximum duration of treatment has been 28 days.
*Pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. By day 7 of age, linezolid clearance and AUC values are similar to those of full-term neonates and older infants.</td></tr>
</table>

Elderly patients:

No dose adjustment is required.

Patients with renal insufficiency:
No dose adjustment is required (see section 5.2 Pharmacokinetic properties).

Patients with severe renal insufficiency (i.e. CL_{CR} < 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 of linezolid in patients with severe renal insufficiency, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

As approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by haemodialysis, but the concentrations of these metabolites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore, linezolid should be used with special caution in patients with severe renal insufficiency who are undergoing dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

To date, there is no experience of linezolid administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than haemodialysis).

Patients with hepatic insufficiency:

No dose adjustment is required. However, there are limited clinical data and it is recommended that linezolid should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk (see section 5.2 Pharmacokinetic properties).

Paediatric population:

Recommended dosages for pediatric patients, please refer to the table above.

Linezolid Injection

Administer linezolid injection by intravenous infusion over a period of 30 to 120 minutes. Do not use the intravenous infusion bag in series connections. Do not introduce additives into the intravenous solution. If linezolid injection is to be given concomitantly with another drug, each drug should be given separately, in accordance with the recommended dosage and route of administration for each product.

Linezolid injection was physically incompatible with the following drugs when combined in simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, phenytoin sodium, erythromycin lactobionate and trimethoprim-sulfamethoxazole.

Linezolid injection was chemically incompatible when combined with ceftriaxone sodium.

Compatible Infusion Solutions:
5% Glucose Injection
0.9% Sodium Chloride Injection
Lactated Ringer's Injection

4.3 Contraindications

Linezolid is contraindicated in patients who have previously demonstrated hypersensitivity to linezolid or any of the other product components.

Monoamine Oxidase Inhibitors
Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine, isocarboxazid) or within two weeks of taking any such medicinal product.

Potential Interactions Producing Elevation of Blood Pressure
Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine, phenylpropanolamine), vasopressive 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
Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine or buspirone (see section 4.5 Interaction with other medicinal products and other forms of interaction).

4.4 Special warnings and precautions for use

Pseudomembranous Colitis
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid, and may range in severity from mild to life-threatening.

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

Clostridium difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated.

Myelosuppression

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pretreatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than younger patients. Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis and in patients with moderate to severe hepatic impairment. 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 or moderate to severe hepatic impairment; receive more than 10-14 days of therapy or those with chronic infection who have received previous or concomitant antibiotic therapy. Linezolid should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible.

Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression.

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.

Lactic acidosis

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

Peripheral and optic neuropathy

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

All patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary. Visual function should be monitored in all patients taking linezolid for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with linezolid.

If peripheral or optic neuropathy occurs, the continued use of Linezolid should be weighed against the potential risks.

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.

Convulsions

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

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) and opioids have been reported (See section 4.3 and 4.5). Co-administration of linezolid and serotonergic agents is therefore contraindicated (see section 4.3) except where administration of linezolid and concomitant serotonergic agents is essential. In those cases patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur.

Linezolid has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

Hyponatremia and/or Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) have been observed in some patients treated with linezolid. It is recommended that serum sodium levels be monitored regularly in the elderly, in patients taking diuretics, and in other patients at risk of hyponatremia.

In healthy volunteers, co-administration of rifampin with linezolid resulted in a 21% decrease in linezolid Cmax and a 32% decrease in linezolid AUC (see section 4.5 Interaction with other medicinal products and other forms of interaction). The clinical significance of this interaction is unknown.

Use in Gram-negative Pathogens
Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected. Linezolid should be used with special caution in patients at high risk for life-threatening systemic infections, such as those with infections related to central venous catheters in intensive care units. Linezolid is not approved for the treatment of patients with catheter-related bloodstream infections.

Mortality imbalance in a clinical trial in patients with catheter-related Gram positive bloodstream infections

An open-label, randomized clinical trial was conducted in adult patients with catheter-related Gram-positive bloodstream infections comparing linezolid (600 mg q12h IV/PO) to vancomycin 1 g IV q12h or oxacillin 2 g IV q6h/dicloxacillin 500 mg PO q6h with a treatment duration of 7 to 28 days. The mortality rates in this study were 78/363 (21.5%) and 58/363 (16.0%) on linezolid and the comparator, respectively. Based on results from a logistic regression, the estimated odds ratio is 1.426 [95% CI 0.970, 2.098]. While causality has not been established, this observed imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogen were identified at baseline. Patients randomized to linezolid who had only a Gram-positive infection at baseline, including the subgroup of patients with Gram-positive bacteremia experienced a survival rate similar to the comparator.

Mitochondrial dysfunction

Linezolid inhibits mitochondrial protein synthesis. Adverse events, such as lactic acidosis, anaemia and neuropathy (optic and peripheral), may occur as a result of this inhibition; these events are more common when the drug is used longer than 28 days.

Monoamine oxidase inhibitors

Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Use with tyramine-rich foods

Patients should be advised against consuming large amounts of tyramine rich foods (see section 4.5).

Development of Drug-Resistant Bacteria

Prescribing LINEZAN in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Superinfection

The effects of linezolid therapy on normal flora have not been evaluated in clinical trials.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. For example, approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

Special populations

Linezolid should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk (see sections 4.2 and 5.2).

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk (see sections 4.2 and 5.2).

Impairment of fertility

Linezolid reversibly decreased fertility and induced abnormal sperm morphology in 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).

Clinical trials

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

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

Excipients

Each ml of the solution contains 45.7 mg (i.e. 13.7 g/300 ml) glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance. Each ml of solution also contains 0.38 mg (114 mg/300 ml) sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

Information for Patients

Patients should be advised that:

- Linezan may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- They should avoid consuming food with high tyramine content.
- They should inform their physician if taking medications containing pseudoephedrine HCl or phenylpropanolamine HCl, such as cold remedies and decongestants.

• They should inform their physician if taking serotonin re-uptake inhibitors or other antidepressants.
• They should inform their physician if they experience changes in vision.
• They should inform their physician if they have a history of seizures.
• Diarrhea is a common problem caused by antibiotics, which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

4.5 Interaction with other medicinal products and other forms of interaction

Drugs metabolised by cytochrome P450
Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not induce or inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced drug interactions are expected with linezolid. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Monoamine oxidase inhibitors
Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Potential Interactions Producing Elevation of Blood Pressure
A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content (e.g., mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

A reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects. A similar study has not been conducted in hypertensive patients. The interaction studies conducted in normotensive subjects evaluated the blood pressure and heart rate effects of placebo, PPA or PSE alone, linezolid alone, and the combination of steady-state linezolid (600 mg q12h for 3 days) with two doses of PPA (25 mg) or PSE (60 mg) given 4 hours apart. Heart rate was not affected by any of the treatments.

Blood pressure was increased with both combination treatments. Maximum blood pressure levels were seen 2 to 3 hours after the second dose of PPA or PSE and returned to baseline 2 to 3 hours after peak. The results of the PPA study follow, showing the mean (and range) maximum systolic blood pressure in mm Hg: placebo = 121 (103 to 158); linezolid alone = 120 (107 to 135); PPA alone = 125 (106 to 139); PPA with linezolid = 147 (129 to 176). The results from the PSE study were similar to those in the PPA study. The mean maximum increase in systolic blood pressure over baseline was 32 mm Hg (range: 20-52 mm Hg) and 38 mm Hg (range: 18-79 mm Hg) during co-administration of linezolid with pseudoephedrine or phenylpropanolamine, respectively. Initial doses of adrenergic agents, such as dopamine or dopamine agonists, should be reduced and 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. The effects of other serotonin reuptake inhibitors have not been studied.

Post marketing experience: there has been one report of a patient experiencing serotonin syndrome-like effects while taking linezolid and dextromethorphan which resolved on discontinuation of both medications.

During clinical use of linezolid with serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), cases of serotonin syndrome have been reported. Therefore, while co-administration is contraindicated (see section 4.3), management of patients for whom treatment with linezolid and serotonergic agents is essential, is described in section 4.4.

Use with tyramine-rich foods
A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100mg. 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).

Antibiotics
The pharmacokinetics of linezolid were not altered when administered together with either aztreonam or gentamicin. The effect of rifampicin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the linezolid Cmax 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 (see section 4.4 Special warnings and precautions for use).

Warfarin
When warfarin was added to linezolid therapy at steady-state, there was a 10% reduction in mean maximum INR on co-administration with a 5% reduction in AUC INR. There are insufficient data from patients who have received warfarin and linezolid to assess the clinical significance, if any, of these findings.

4.6 Fertility, pregnancy and lactation

Reproductive studies performed in mice and rats treated with linezolid showed no evidence of teratogenic effects. Mild fetal toxicity was observed in mice only at maternally toxic dose levels. In rats, fetal toxicity was manifested as decreased fetal body weights and reduced ossification of sternebrae (which is often seen in association with decreased body weights). Reduced pup survival and mild maturational delays occurred in rats. When mated, these same pups showed evidence of a reversible, dose-related increase in pre-implantation loss. There are no adequate and well-controlled studies in pregnant women. Therefore, linezolid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Linezolid decreased the fertility of male rats.

Linezolid transferred into the breast milk of lactating laboratory rats. It is not known whether linezolid is excreted in human milk. Therefore, caution should be exercised when linezolid is administered to a nursing woman.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or symptoms of visual impairment (as described in section 4.4 and 4.8) whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8 Undesirable effects

ADRs by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	**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**	**Frequency Not Known (cannot be estimated from the available data)**
Infections and infestations		Moniliasis				
Blood and lymphatic system disorders		Thrombocytopenia*, Anemia*	Pancytopenia* , Leucopenia*	Sideroblastic anemia*		
Immune system disorders				Anaphylaxis*		
Metabolism and nutrition disorders				Lactic acidosis*		
Nervous system disorders		Headache	Convulsions*, Peripheral neuropathy*, Taste alteration			
Eye disorders			Optic neuropathy*			
Gastrointestinal disorders		Vomiting, Diarrhea, Nausea, Abdominal pain including abdominal cramps	Abdominal cramps[#], Abdominal distension, Tongue discoloration*	Superficial tooth discoloration*		
Skin and subcutaneous tissue disorders		Rash*	Bullous skin disorders, Severe cutaneous adverse reactions, Angioedema*	Hypersensitivity vasculitis*		Toxic epidermal necrolysis*, Stevens-Johnson syndrome*
Investigations		Abnormal liver function tests	Abnormal hematology tests			

*ADR identified post-marketing

The ADR Abdominal cramps is defined by MedDRA LLT and not by PT.

4.9 Overdose

No specific antidote is known.

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

Supportive care is advised together with maintenance of glomerular filtration. Approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

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

General Properties
Pharmacotherapeutic group (ATC code): J01XX08.

Linezolid is a synthetic, antibacterial agent which belongs to a new class of antibiotics, the oxazolidinones, with *in vitro* activity against aerobic Gram-positive bacteria, certain Gram-negative bacteria and anaerobic microorganisms. It selectively inhibits bacterial protein synthesis via a unique mechanism of action. Linezolid 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. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for majority of strains.

The *in vitro* postantibiotic effect (PAE) of linezolid for *Staphylococcus aureus* was approximately 2 hours. When measured in animal models, the *in vivo* PAE was 3.6 to 3.9 hours for *Staphylococcus aureus* and *Streptococcus pneumoniae*, respectively. In animal studies, the key pharmacodynamic parameter for efficacy was the time that the linezolid plasma levels exceeded the minimum inhibitory concentration (MIC) of the infecting organism. Linezolid was efficacious when plasma levels exceeded the MIC of the infecting organism for a minimum of 40% of the dosing interval.

Linezolid has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections, as described in section 4.1 Therapeutic indications.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecium (vancomycin-resistant strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus pneumoniae (penicillin-susceptible strains only)
Streptococcus pyogenes

The following *in vitro* data are available, but their clinical significance is unknown. At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and effectiveness of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.
Aerobic and facultative Gram-positive microorganisms
Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (vancomycin-susceptible strains)

Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Streptococcus pneumoniae (penicillin-resistant strains)
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms
Pasteurella multocida

Breakpoints

The following MIC breakpoints separate susceptible from non-susceptible isolates:

Pathogen	Susceptibility Interpretive criteria					
	MIC in micrograms/ml			Disk diffusion (Zone diameters in mm)		
	S	I	R	S	I	R
Enterococcus species	≤2	4	≥8	≥23	21-22	≤20
Staphylococcus species	≤4	--		≥21		--
Streptococcus pneumoniae	≤2	--		≥21	--	--
Streptococcus species other than *S. pneumoniae*	≤2	--		≥21	--	--
The current absence of data on resistant strains precludes defining any categories other than "susceptible". Strains yielding MIC results suggestive of a "non-susceptible" category should be submitted to a reference laboratory for further testing.						

The studies used to define the above breakpoints were standard NCCLS (National Committee for Clinical Laboratory Standards) microdilution and agar diffusion methods.

Susceptibility
The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections.

Resistance
Linezolid's mechanism of action differs from that of other antibiotic classes (e.g., the aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol). Therefore, there is no cross resistance between linezolid and these classes of drug. Linezolid is active against pathogens that are susceptible or resistant to such antibiotics.

5.2 Pharmacokinetic properties

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

Absorption
Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing. Absolute oral bioavailability of linezolid (oral and intravenous dosing in a crossover study) is complete (approximately 100%). Absorption is not significantly affected by food and absorption from the oral suspension is similar to that achieved with the film-coated 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.

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

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

Biotransformation

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

Elimination

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

Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. A small degree of non-linearity in clearance is observed with increasing doses of linezolid. This appears to be due to lower renal and non-renal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.

Special Populations

Patients with renal insufficiency: After single doses of 600 mg, there was a 7-8 fold increase in exposure to the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e. creatinine clearance < 30 ml/min). However, there was no increase in AUC of parent drug. Although there is some removal of the major metabolites of linezolid by haemodialysis, metabolite plasma levels after single 600 mg doses were still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

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

The clinical significance of these observations has not been established as limited safety data are currently available (see sections 4.2 and 4.4).

Patients with hepatic insufficiency: Limited data indicate that the pharmacokinetics of linezolid, PNU-142300 and PNU-142586 are not altered in patients with mild to moderate hepatic insufficiency (i.e. Child-Pugh class A or B). The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e. Child-Pugh class C) have not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism (see sections 4.2 and 4.4).

Paediatric population (< 18 years old):

In children 1 week to 12 years old, administration of 10 mg/kg every 8 hours daily gave exposure approximating to that achieved with 600 mg twice daily in adults.

In neonates up to 1 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 paediatric patients with ventriculoperitoneal shunts who were administered linezolid 10 mg/kg either 12 hourly or 8 hourly, variable cerebrospinal fluid (CSF) linezolid concentrations were observed following either single or multiple dosing of linezolid. Therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empirical treatment of paediatric patients with central nervous system infections is not recommended.

Elderly patients: The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 and over.

Female patients: Females have a slightly lower volume of distribution than males and the mean clearance is reduced by approximately 20% when corrected for body weight. Plasma concentrations are higher in females and this can partly be attributed to body weight differences. However, because the mean half life of linezolid is not significantly different in males and females, plasma concentrations in females are not expected to substantially rise above those known to be well tolerated and, therefore, dose adjustments are not required.

5.3 Preclinical safety data

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those expected in humans. In sexually mature animals these effects were reversible. The reversible effects on fertility were mediated by altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. The presence of abnormal sperm in the epididymis was accompanied by epithelial cell hypertrophy and hyperplasia. Epididymal hypertrophy was not observed in dogs treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

Sexually mature male rats showed slightly decreased fertility following oral treatment as juveniles throughout most of their period of sexual development (50 mg/kg/day from postnatal days 7 to 36, and 100 mg/kg/day from days 37 to 55), at exposures up to 1.7 times the mean AUC in pediatric patients aged 3 months to 11 years. Decreased fertility was not observed following shorter treatment periods in utero through the early neonatal period (gestation day 6 through postnatal day 5), neonatal exposure (postnatal days 5 to 21), or juvenile exposure (postnatal days 22 to 35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats following treatment on postnatal days 22 to 35.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 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.

Linezolid was also not teratogenic in rabbits when administered twice daily at total oral doses up to 15 mg/kg/day (0.06 times the clinical exposure, based on AUC). Maternal toxicity (clinical signs, reduced body weight gain and food consumption) occurred at 5 and 15 mg/kg/day, and reduced fetal body weight occurred at 15 mg/kg/day. Linezolid exposures were low due to the characteristic sensitivity of rabbits to antibiotics.

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

Linezolid produced reversible myelosuppression in adult and juvenile rats and dogs.

In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 male rats administered Linezolid at 80 mg/kg/day for 6 months, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The nerve degeneration observed was microscopically comparable to a spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of a common background change.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose (Dextrose) monohydrate
Sodium citrate dihydrate
Citric acid anhydrous
Hydrochloric acid (10%) or Sodium hydroxide (10%)
Water for injections

6.2 Incompatibilities

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. Similarly, if the same intravenous line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following linezolid administration with a compatible infusion solution (see section 6.6).

Linezolid solution for infusion is known to be physically incompatible when combined in simulated Y-site administration with the following compounds: amphotericin B, chlorpromazine hydrochloride, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and sulphamethoxazole/trimethoprim. Additionally, it is chemically incompatible with ceftriaxone sodium.

6.3 Shelf life

Before opening: 3 years

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user (CPMP/QWP/159/96).

6.4 Special precautions for storage

Store in the original package in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Single use, ready to use, polypropylene film infusion bag sealed within polycarbonate elastomere connector inside a foil laminate overwrap. The infusion bag holds 300 ml solution for infusion which contains 600 mg Linezolid.

Each infusion bag is placed in a foil laminate overwrap accompanied by the appropriate instruction leaflet. Each box contains 1*, 2**, 5, 10, 20 or 25 infusion bags.

Note:
The above boxes may also be supplied in "hospital" packs of:
*5, 10 or 20
**3, 6 or 10
Not all package sizes may be marketed.

6.6 Instructions for use, handling and disposal

For single use only. Remove overwrap only when ready to use, then check for minute leaks by squeezing the bag firmly. If the bag leaks, do not use as sterility may be impaired. The solution should be visually inspected prior to use and only clear solutions, without particles should be used. Do not use these bags in series connections. Any unused solution must be discarded. No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not reconnect partially used bags.

Linezan solution for infusion is compatible with the following solutions: 5% glucose intravenous infusion, 0.9% sodium chloride intravenous infusion, Ringer-lactate solution for injection (Hartmann's solution for injection).

7. PRODUCT OWNER & REGISTRANT

PRODUCT OWNER

ANFARM HELLAS S.A.

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8. REGISTRATION NUMBER

9. DATE OF REGISTRATION

10. DATE OF REVISION OF THE TEXT

December 2023