

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Linezolid Teva 600 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 600 mg linezolid.

Excipients

Each film-coated tablet contains 185.73 mg lactose (as lactose monohydrate).

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

White, film-coated oblong tablet, debossed with "93" on one side and "7490" on the other side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

When oral therapy is appropriate:

- *Nosocomial pneumonia*

Community-acquired pneumonia

Linezolid is indicated for the treatment of community-acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram-positive bacteria. In determining whether linezolid is an appropriate treatment, the results of microbiological tests or information on the prevalence of resistance to antibacterial agents among Gram-positive bacteria should be taken into consideration (see section 5.1 for the appropriate organisms).

Linezolid is not active against infections caused by Gram-negative pathogens. Specific therapy against Gram-negative organisms must be initiated concomitantly if a Gram-negative pathogen is documented or suspected.

- *Complicated skin and soft tissue infections (see section 4.4)*

Linezolid 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.

Linezolid is not active against infections caused by Gram-negative pathogens. Linezolid should only be used in patients with complicated skin and soft tissue infections with known or possible co-infection with Gram-negative organisms if there are no alternative treatment options available (see section 4.4). In these circumstances treatment against Gram-negative organisms **must** be initiated concomitantly.

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

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

4.2 Posology and method of administration

If and where available, linezolid solution for infusion, film-coated tablets or oral suspension may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to either oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as linezolid has an oral bioavailability of approximately 100%.

Recommended dosage and duration of treatment for adults

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

The following recommendations for duration of therapy reflect those used in the clinical trials. Shorter treatment regimens may be suitable for some types of infection but have not been evaluated in clinical trials.

The maximum treatment duration is 28 days. The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established (see section 4.4).

No increase in the recommended dosage or duration of treatment is required for infections associated with concurrent bacteraemia.

The dose recommendations are as follows:

Infections	Dosage	Duration of treatment
Nosocomial pneumonia	600 mg twice daily	10–14 consecutive days
Community-acquired pneumonia	600 mg twice daily	10–14 consecutive days
Complicated skin and soft tissue infections	600 mg twice daily	10–14 consecutive days

Children

There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old) to establish dosage recommendations (see sections 5.1 and 5.2). Therefore, until further data are available, use of linezolid in this age group is not recommended.

Elderly patients

No dose adjustment is required.

Patients with renal insufficiency

No dose adjustment is required (see sections 4.4 and 5.2).

Patients with severe renal insufficiency (i.e. creatinine clearance (ClCr) < 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 sections 4.4 and 5.2).

Method of administration

The recommended linezolid dosage should be administered twice daily.

Route of administration

Oral use.

The film-coated tablets may be taken with or without food.

4.3 Contraindications

Hypersensitivity to linezolid or to any of the excipients (see section 6.1).

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

Unless there are facilities available for close observation and monitoring of blood pressure, linezolid should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant treatment:

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

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration (see section 4.6).

4.4 Special warnings and precautions for use

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAO); however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant treatments 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 sections 4.3 and 4.5).

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

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 haematological parameters have risen toward pre-treatment levels. The risk of these effects appears to be related to the duration of treatment. 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 treatment 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.

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.

Excess mortality was seen in patients treated with linezolid, relative 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 study treatment. 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 linezolid 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). In these circumstances treatment against Gram-negative organisms must be initiated concomitantly.

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.

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).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent. In cases of suspected or verified antibiotic-associated colitis, discontinuation of linezolid may be warranted. Appropriate management measures should be instituted.

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, have been reported in association with the use of nearly all antibiotics including linezolid and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of linezolid. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including linezolid, should be discontinued and adequate therapeutic measures should be initiated immediately. Agents inhibiting peristalsis are contraindicated in this situation.

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 related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

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

Peripheral neuropathy and optic neuropathy, 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. If any patients are taking linezolid for longer than the recommended 28 days, their visual function should be regularly monitored.

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

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.

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 (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 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).

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose–galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Linezolid is a reversible, non–selective inhibitor of monoamine oxidase (MAO). There are very limited data from interaction studies and on the safety of linezolid when administered to patients on concomitant agents that might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see section 4.3).

In normotensive healthy volunteers, linezolid enhanced the increases in blood pressure caused by pseudoephedrine and phenylpropanolamine hydrochloride.

Co–administration of linezolid with either pseudoephedrine or phenylpropanolamine resulted in mean increases in systolic blood pressure of the order of 30–40 mmHg, compared with 11–15 mmHg increases with linezolid alone, 14–18 mmHg with either pseudoephedrine or phenylpropanolamine alone and 8–11 mmHg with placebo. Similar studies in hypertensive subjects have not been conducted. It is recommended that doses of agents with a vasopressive action, including dopaminergic agents, should be carefully titrated to achieve the desired response when co–administered with linezolid.

The potential 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 which resolved on discontinuation of both agents.

During clinical use of linezolid with serotonin re–uptake inhibitors, 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.

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).

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450–induced interactions are expected with linezolid.

The effect of rifampicin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the linezolid C_{max} and AUC by a mean 21% [90% CI: 15, 27] and a mean 32% [90% CI: 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown.

When warfarin was added to linezolid therapy at steady–state, there was a 10% reduction in mean maximum international normalized ratio (INR) on co–administration with a 5% reduction in area under the curve (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

There are no adequate data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). A potential risk for humans exists.

Linezolid should not be used during pregnancy unless clearly necessary *i.e.* only if the potential benefit outweighs the theoretical risk.

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

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness whilst receiving linezolid and should be advised not to drive or operate machinery if dizziness occurs.

4.8 Undesirable effects

The table below provides a listing of adverse drug reactions occurring at frequencies $\geq 0.1\%$ in clinical studies that enrolled more than 2,000 adult patients who received the recommended linezolid doses for up to 28 days.

Approximately 22% of patients experienced adverse reactions; those most commonly reported were headache (2.1%), diarrhoea (4.2%), nausea (3.3%) and candidiasis (particularly oral [0.8%] and vaginal [1.1%] candidiasis, see table below).

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

Additional adverse reactions reported from post-marketing experience are included in the table with frequency category 'not known', since the actual frequency cannot be estimated from the available data.

Adverse drug reactions occurring at frequencies > 0.1%		
Infections and infestations	Common	Candidiasis (particularly oral and vaginal candidiasis) or fungal infections
	Uncommon	Vaginitis
	Not known	Antibiotic-associated colitis*, pseudomembranous colitis.
Blood and lymphatic system disorders	Uncommon	Eosinophilia, leucopenia*, neutropenia, thrombocytopenia*
	Not known	Myelosuppression*, pancytopenia*, anaemia* [†]
Immune disorders	Not known	Anaphylaxis
Metabolism and nutrition disorders	Not known	Lactic acidosis*
Psychiatric disorders	Uncommon	Insomnia
Nervous system	Common	Headache, taste perversion (metallic taste)
	Uncommon	Dizziness, hypoaesthesia, paraesthesia

<i>disorders</i>	Not known	Serotonin syndrome**, convulsions*, peripheral neuropathy*
<i>Eye disorders</i>	Uncommon	Blurred vision
	Not known	Optic neuropathy*
<i>Ear and labyrinth disorders</i>	Uncommon	Tinnitus
<i>Vascular disorders</i>	Uncommon	Hypertension, phlebitis/thrombophlebitis
<i>Gastrointestinal disorders</i>	Common	Diarrhoea, nausea, vomiting
	Uncommon	Localised or general abdominal pain, constipation, dry mouth, dyspepsia, gastritis, glossitis, loose stools, pancreatitis, stomatitis, tongue discolouration or disorder
	Not known	Superficial tooth discolouration
<i>Hepato-biliary disorders</i>	Common	Abnormal liver function test
<i>Skin and subcutaneous tissue disorders</i>	Uncommon	Dermatitis, diaphoresis, pruritus, rash, urticaria
	Not known	Bullous disorders such as those described as Stevens-Johnson syndrome, angioedema, alopecia
<i>Renal and urinary disorders</i>	Uncommon	Polyuria
<i>Reproductive system and breast disorders</i>	Uncommon	Vulvovaginal disorder
<i>General disorders and administration site conditions</i>	Uncommon	Chills, fatigue, fever, increased thirst, localised pain
<i>Investigations</i>		
Chemistry	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
Common $\geq 1/100$ to $< 1/10$		
Uncommon $\geq 1/1,000$ to $< 1/100$		

* See section 4.4

** See sections 4.3 and 4.5

† See below

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

During clinical trials, a single case of arrhythmia (tachycardia) was reported as substance-related.

† In controlled clinical trials where linezolid was administered for up to 28 days, less than 0.1% of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for > 28 days. The proportion of cases reporting substance-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for > 28 days.

Safety data from clinical studies based on more than 500 paediatric patients (from birth to 17 years) do not reveal any new observations indicating that the safety profile of linezolid for paediatric patients differs from that for adult patients.

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

Pharmacotherapeutic group: Other antibacterials.

ATC code: J01X X08

General properties

Linezolid is a synthetic antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. It has *in vitro* activity against aerobic and anaerobic Gram-positive bacteria. Linezolid selectively inhibits bacterial protein synthesis *via* a unique mechanism of action. Specifically, it binds to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

The *in vitro* post-antibiotic effect (PAE) of linezolid for *Staphylococcus aureus* was 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 pharmacodynamic parameter for efficacy was the time for which the linezolid plasma level exceeded the minimum inhibitory concentration (MIC) for the infecting organism.

Breakpoints

Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and enterococci are Susceptible ≤ 4 mg/l and Resistant > 4 mg/l. For streptococci (including *S. pneumoniae*) the breakpoints are Susceptible ≤ 2 mg/l and Resistant > 4 mg/l.

Non-species-related MIC breakpoints are Susceptible ≤ 2 mg/l and Resistant > 4 mg/l. Non-species-related breakpoints have been determined mainly on the basis of pharmacokinetic/pharmacodynamic data and are independent of MIC distributions of specific species. They are for use only for organisms that have not been given a specific breakpoint and not for those species where susceptibility testing is not recommended.

Susceptibility

The relevance of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Category		
<u>Susceptible organisms</u>	Gram-positive aerobes:	<i>Enterococcus faecalis</i> <i>Enterococcus faecium</i> * <i>Staphylococcus aureus</i> * Coagulase-negative staphylococci <i>Streptococcus agalactiae</i> * <i>Streptococcus pneumoniae</i> * <i>Streptococcus pyogenes</i> * Group C streptococci Group G streptococci
	Gram-positive anaerobes:	<i>Clostridium perfringens</i> <i>Peptostreptococcus anaerobius</i> <i>Peptostreptococcus species</i>
<u>Resistant organisms</u>	-	<i>Haemophilus influenzae</i> <i>Moraxella catarrhalis</i> <i>Neisseria species</i> <i>Enterobacteriaceae</i> <i>Pseudomonas species</i>

*Clinical efficacy has been demonstrated for susceptible 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 gene encoding 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.

Information from clinical trialsStudies in the paediatric population

In an open study, the efficacy of linezolid (10 mg/kg q8h) was compared to vancomycin (10–15 mg/kg q6h – 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

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 [standard deviation]) 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.

Metabolism

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 substance (30%) and PNU-142300 (10%). Virtually no parent substance 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 substance. 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).

Children and adolescents (< 18 years old)

There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old) and therefore, use of linezolid in this age group is not recommended (see section 4.2). Further studies are needed to establish safe and effective dosage recommendations.

Pharmacokinetic studies indicate that after single and multiple doses in children (1 week to 12 years), linezolid clearance (based on kg body weight) was greater in paediatric patients than in adults, but decreased with increasing age.

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

In 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 600mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that observed in adults receiving the same dosage.

In paediatric patients with ventriculoperitoneal shunts who were administered linezolid 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. However, these effects did not reverse in juvenile animals treated with linezolid for nearly the entire period of sexual maturation. Abnormal sperm morphology in testis of adult male rats, and epithelial cell hypertrophy and hyperplasia in the epididymis were noted. Linezolid appeared to affect the maturation of rat spermatozoa. Supplementation of testosterone had no effect on linezolid-mediated fertility effects. Epididymal hypertrophy was not observed in dogs treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 times or equivalent, respectively, to those 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 myelosuppression in rats and dogs.

In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphological 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 treatment 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

Tablet core

Lactose monohydrate

Lactose monohydrate, spray-dried

Maize starch

Crospovidone

Hydroxypropylcellulose

Crosscarmellose sodium

Magnesium stearate

Film-coating

Hypromellose 2910 5cP (E464)

Macrogol 400

Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/PVdC–aluminium blisters.

OPA /Alu/PVC–aluminium blisters

Pack sizes: 1, 10, 20, 30, 50, 60, 100 film–coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

7 MARKETING AUTHORISATION HOLDER

Teva Pharma BV

Computerweg 10

3542 DR Utrecht

The Netherlands

8 MARKETING AUTHORISATION NUMBER

PA 749/91/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 4th June 2010

10 DATE OF REVISION OF THE TEXT