**PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE**

**SCHEDULING STATUS**

**S4**

## 1. NAME OF THE MEDICINE

**LINEZOLID 600 mg/300 ml ASPEN solution for infusion**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LINEZOLID 600 mg/300 ml ASPEN solution for infusion contains 2 mg of linezolid per ml

Contains sugar: Glucose monohydrate 50,24 mg/ml

Each ml contains 0,38 mg (114 mg/300 ml) sodium.

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

LINEZOLID 600 mg/300 ml ASPEN solution for infusion is a clear, colourless to yellow solution.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

LINEZOLID 600 mg/300 ml ASPEN is indicated for the treatment of patients with the following infections caused by susceptible strains of the designated micro-organisms (see section 5).
LINEZOLID 600 mg/300 ml ASPEN is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy must be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see section 4.4).

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

- **Nosocomial pneumonia** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumonia*e (including multi-drug resistant *S. pneumoniae* (MDRSP) strains).

- **Complicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. LINEZOLID 600 mg/300 ml ASPEN has not been studied in the treatment of decubitus ulcers.

- **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin susceptible and -resistant strains), *Streptococcus pyogenes*.

- **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multi-drug resistant *S. pneumoniae* (MDRSP) strains), including cases with concurrent bacteraemia, or *Staphylococcus aureus* (methicillin-susceptible and -resistant strains).

Due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with LINEZOLID 600 mg/300 ml ASPEN in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to linezolid.

Therapy may be instituted empirically while awaiting results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

## 4.2. Posology and method of administration

**Posology**

LINEZOLID 600 mg/300 ml ASPEN solution for infusion 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 the oral formulation has bioavailability of approximately 100 %.

The recommended LINEZOLID 600 mg/300 ml ASPEN dosage should be administered IV as described in the tables below.

**Table A: Adult and Adolescent (12 years and older) patients:**

| Infections (including those associated with concurrent bacteraemia) | Dosage and route of administration | Duration of treatment |
|---|---|---|
| Community-acquired pneumonia, including concurrent bacteraemia | 600 mg IV every 12 hours | 10 to 14 consecutive days |
| Nosocomial pneumonia, including concurrent bacteraemia | | |
| Skin and soft tissue infections, including concurrent bacteraemia | 600 mg IV every 12 hours depending on clinical severity | |
| Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia | 600 mg IV every 12 hours | 14 to 28 consecutive days |

**Table B: Paediatric Patients (birth* through to 11 years):**

| Infections (including those associated with concurrent bacteraemia) | Dosage and route of administration | Duration of treatment |
|---|---|---|
| Community-acquired pneumonia, including concurrent bacteraemia | 10 mg/kg IV every 8 hours | 10 to 14 consecutive days |
| Nosocomial pneumonia, including concurrent bacteraemia | | |
| Skin and soft tissue infections, including concurrent bacteraemia | | |

| | | |
|---|---|---|
| Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia | 10 mg/kg IV every 8 hours | 14 to 28 consecutive days |

*Pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have lower systemic LINEZOLID 600 mg/300 ml ASPEN clearance values and larger AUC values than many full-term neonates and older infants. By day 7 of age, LINEZOLID 600 mg/300 ml ASPEN clearance and AUC values are similar to those of full-term neonates and older infants.

**Special populations**

*Elderly population*

No dose adjustment is necessary.

*Renal impairment*

No dose adjustment is required.

*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 600 mg/300 ml ASPEN in patients with severe renal insufficiency, LINEZOLID 600 mg/300 ml ASPEN 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 LINEZOLID 600 mg/300 ml ASPEN dose is removed during 3 hours of haemodialysis, LINEZOLID 600 mg/300 ml ASPEN should be given after dialysis in patients receiving such treatment. The primary metabolites of LINEZOLID 600 mg/300 ml ASPEN 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 600 mg/300 ml ASPEN 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 600 mg/300 ml ASPEN administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than haemodialysis).

*Hepatic impairment*

No dose adjustment is required. However, there are limited clinical data and it is recommended that LINEZOLID 600 mg/300 ml ASPEN should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.

**Paediatric population**

Currently available data are described in section 4.2 Table B: Paediatric patients (birth* through to 11 years).

**Method of administration**

For intravenous administration.

The solution for infusion should be administered over a period of 30 to 120 minutes.

For instructions on administration and other handling, see section 6.6.

## 4.3. Contraindications

LINEZOLID 600 mg/300 ml ASPEN is contraindicated in:

- Patients with hypersensitivity to linezolid or to any excipients in LINEZOLID 600 mg/300 ml ASPEN (see section 6.1).
- **Monoamine oxidase inhibitors**

LINEZOLID 600 mg/300 ml ASPEN should not be used in patients taking any medicines which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within two weeks of taking any such medicine.

- **Potential interactions producing elevation of blood pressure**

  Unless patients are monitored for potential increases in blood pressure, LINEZOLID 600 mg/300 ml ASPEN should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medicines: directly and indirectly acting sympathomimetic medicines (e.g., pseudoephedrine, phenylpropanolamine), vasopressive medicines (e.g., epinephrine, norepinephrine), dopaminergic medicines (e.g., dopamine, dobutamine) (see sections 4.4 and 4.5).

- **Potential serotonergic interactions**

  Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, LINEZOLID 600 mg/300 ml ASPEN 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-$HT_1$ receptor agonists (triptans), meperidine or buspirone (see sections 4.4 & 4.5).

## 4.4. Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

It is recommended that therapy with LINEZOLID 600 mg/300 ml ASPEN should be initiated in a hospital environment following guidance from appropriate specialists.

*Myelosuppression*

Reversible myelosuppression (anaemia, thrombocytopenia**,** leukopenia, and pancytopenia) that may be dependent on duration of therapy has been reported in some patients receiving LINEZOLID 600 mg/300 ml ASPEN.

In cases where the outcome is known, the affected haematological parameters have risen towards pre-treatment levels when linezolid, as in LINEZOLID 600 mg/300 ml ASPEN was discontinued. Complete blood counts should be monitored weekly in patients who receive linezolid, as in LINEZOLID 600 mg/300 ml ASPEN for longer than two weeks, particularly those with pre-existing myelosuppression, those receiving concomitant medicines that produce bone marrow suppression, or those with a chronic infection who have received previous antibiotic therapy. Discontinuation of therapy should be considered in patients who develop or who have a worsening of myelosuppression.

*Peripheral neuropathy and optic neuropathy*

Peripheral neuropathy and optic neuropathy have been reported in patients treated with LINEZOLID 600 mg/300 ml ASPEN, primarily those patients treated for longer than the maximum recommended duration of 28 days. When outcome was known, recovery was reported in some cases following LINEZOLID 600 mg/300 ml ASPEN withdrawal*.* In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with LINEZOLID 600 mg/300 ml ASPEN for less than 28 days.

If symptoms of visual impairment appear, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, prompt ophthalmic evaluation is recommended. Visual function should be monitored in all patients taking LINEZOLID 600 mg/300 ml ASPEN 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 600 mg/300 ml ASPEN. If peripheral

or optic neuropathy occurs, the continued use of LINEZOLID 600 mg/300 ml ASPEN in these patients should be weighed against the potential risks.

*Duration of treatment*

The safety and effectiveness of LINEZOLID 600 mg/300 ml ASPEN when administered for periods longer than 28 days have not been established. Treatment prolonged beyond 28 days has been associated with serious adverse effects, including myelosuppression, peripheral neuropathy and optic neuropathy.

*Lactic acidosis*

Lactic acidosis has been reported with the use of LINEZOLID 600 mg/300 ml ASPEN. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving LINEZOLID 600 mg/300 ml ASPEN should receive immediate medical attention.

*Convulsions*

Convulsions have been reported to occur in patients when treated with LINEZOLID 600 mg/300 ml ASPEN. In most of these cases, a history of seizures or risk factors for seizures were reported.

*Serotonin syndrome*

Spontaneous reports of serotonin syndrome associated with the co-administration of LINEZOLID 600 mg/300 ml ASPEN and serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see sections 4.3 and 4.5).

*Antibiotic associated pseudomembranous colitis*

Pseudomembranous colitis has been reported with LINEZOLID 600 mg/300 ml ASPEN and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of this antibacterial medicine.

Mild cases usually respond to medicine discontinuation alone, however, in moderate to severe cases appropriate therapy with a suitable oral antibacterial medicine effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Medicines which delay peristalsis, e.g., opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used.

*Clostridium difficile* associated diarrhoea (CDAD) has been reported with LINEZOLID 600 mg/300 ml ASPEN and may range in severity from mild diarrhoea to fatal colitis. Treatment with LINEZOLID 600 mg/300 ml ASPEN alters the normal flora of the colon leading to overgrowth of *C. difficile.*

*C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines.

*Superinfection*

The use of antibiotics may result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

LINEZOLID 600 mg/300 ml ASPEN 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 600 mg/300 ml ASPEN 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 600 mg/300 ml ASPEN is not approved for the treatment of patients with catheter-related bloodstream infections.

*Uncontrolled hypertension, phaeochromocytoma, carcinoid syndrome, or untreated hyperthyroidism*

LINEZOLID 600 mg/300 ml ASPEN has not been studied in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid syndrome, or untreated hyperthyroidism (see section 4.3).

*Renal insufficiency*

LINEZOLID 600 mg/300 ml ASPEN 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 section 4.2).

*Hepatic insufficiency*

It is recommended that LINEZOLID 600 mg/300 ml ASPEN should be used in patients with severe hepatic insufficiency only when the anticipated benefit is considered to outweigh the theoretical risk (see section 4.2).

*Effects on laboratory tests*
No data available.

*Use in the elderly*

**Paediatric population**

The clearance of linezolid, as in ASPEN LINEZOLID 600 mg/ 300 ml, is most rapid in the youngest age groups (excluding neonates less than 1 week old), resulting in a shorter half-life. As children mature, the clearance of linezolid, as in ASPEN LINEZOLID 600 mg/ 300 ml gradually decreases and by adolescence the clearance values approach those observed for the adult population (see section 4.2).

While medicines clearance in adolescents (ages 12 through 17 years) is usually similar to the clearance in adults, there is wider inter subject variation in this age group compared with adults (see section 5.1 *Pharmacology, Special population, Paediatrics*). Data showed similar efficacy in adult and adolescent patients. Given the wider inter subject variation in adolescents, the slight possibility that high clearance may result in decreased efficacy in some adolescent patients should be considered. The dosage for paediatric patients younger than 12 years of age should be 10 mg/kg every 8 hours, while children 12 years and older should receive the same dose as adult patients, 600 mg every 12 hours (see section 4.2 ).

*Excipients*

LINEZOLID 600 mg/300 ml ASPEN contains 50,24 mg glucose monohydrate per ml. This should be taken into account with patients with diabetes mellitus.

LINEZOLID 600 mg/300 ml ASPEN contains 114 mg sodium per 300 ml bag, equivalent to 5,7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5. Interaction with other medicines and other forms of interaction

LINEZOLID 600 mg/300 ml ASPEN is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not induce or inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced medicine interactions are expected. Medicines such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with LINEZOLID 600 mg/300 ml ASPEN without changes in dosage regimen.

*Antibiotics*

No interactions have been observed in pharmacokinetic studies with either aztreonam or gentamicin.

LINEZOLID 600 mg/300 ml ASPEN is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Clinical studies have shown that coadministration of LINEZOLID 600 mg/300 ml ASPEN with either pseudoephedrine or phenylpropanolamine resulted in mild, reversible enhancement of the pressor responses in normotensive patients. Similar studies in hypertensive subjects have not been conducted. The potential for interaction with sympathomimetic and adrenergic medicines should be considered (see section 4.3). Initial doses of potent vasopressors, such as dopamine and adrenaline (epinephrine), should be reduced and carefully titrated to achieve the desired response when co-administered with LINEZOLID 600 mg/300 ml ASPEN (see section 4.3).

No significant pressor response was observed on receiving both LINEZOLID 600 mg/300 ml ASPEN and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting large 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).

Data have shown that co-administration of LINEZOLID 600 mg/300 ml ASPEN with dextromethorphan was not associated with serotonin syndrome effects (e.g., confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia). The effects of other serotonin uptake inhibitors have not been studied.

Spontaneous reports of serotonin syndrome associated with the co-administration of LINEZOLID 600 mg/300 ml ASPEN and serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported (see section 4.3).

Where administration of LINEZOLID 600 mg/300 ml ASPEN and concomitant serotonergic medicines 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, medical practitioners should consider discontinuation of either one or both medicines. If the concomitant serotonergic medicines is withdrawn, discontinuation symptoms can be observed.

*Rifampicin*

In healthy volunteers, co-administration with ASPEN LINEZOLID 600 mg/ 300 ml resulted in a 21 % decrease in linezolid $C_{max}$ and a 32 % decrease in linezolid AUC. The mechanism of this interaction and its clinical significance are unknown.

## 4.6 Fertility, pregnancy and lactation

The use of LINEZOLID 600 mg/300 ml ASPEN in pregnancy and lactation is contraindicated, as safety has not been demonstrated.

**Pregnancy**

LINEZOLID 600 mg/300 ml ASPEN should not be used in pregnancy, as safety has not been established.

**Breastfeeding**

LINEZOLID 600 mg/300 ml ASPEN is likely to pass into breast milk, therefore breastfeeding should be discontinued prior to administration.

**Fertility**

There is no human fertility data.

## 4.7 Effects on ability to drive and use machines

LINEZOLID 600 mg/300 ml ASPEN may have a moderate influence on the ability to drive or use machines.

Patients should be warned about the potential for dizziness or symptoms of visual impairment (see section 4.4 and 4.8) whilst receiving LINEZOLID 600 mg/300 ml ASPEN and should be advised not to drive or operate machinery if any of these symptoms occurs.

## 4.8 Undesirable effects

*a) Summary of the safety profile*

**Adult patients**

Clinical data from patients who received linezolid for up to 28 days indicated the majority of adverse reactions to linezolid were of mild to moderate intensity, of limited duration and did not require discontinuation of treatment. The adverse reactions were not dose dependent.

Approximately 22 % of patients experienced adverse reactions. Those most commonly reported were headache, diarrhoea, nausea, vomiting, metallic taste, abnormal liver function tests and vaginal moniliasis.

Adverse events considered medicine-related in controlled clinical trials with an incidence of at least 1 % were:

Gastrointestinal disorders: Abdominal pain/cramps/distension, diarrhoea, nausea, vomiting.

Infections and infestations: Moniliasis.

Investigations: Abnormal haematology tests, abnormal liver function tests.

Nervous system disorders: Headache, taste alteration.

| **System organ class** | **Frequent** | **Less frequent** | **Frequency unknown*** (cannot be estimated from the available data) |
|---|---|---|---|
| **Infections and infestations** | Candidiasis (oral and vaginal), fungal infection | Vaginitis | |
| **Blood and the lymphatic system disorders** | | Reversible anaemia, eosinophilia, leukopenia, neutropenia, thrombocytopenia, pancytopenia | Sideroblastic anaemia** |
| **Immune system disorders** | | | Anaphylaxis** |

| | | | |
|---|---|---|---|
| **Metabolism and nutrition disorders** | | Increased serum creatine phosphokinase, hyperglycaemia, lactic acidosis** | |
| **Nervous system disorders** | Headache, taste alteration, | Dizziness, hypoaesthesia, insomnia, paraesthesia, peripheral neuropathy**, convulsions** | Serotonin syndrome** |
| **Eye disorders** | | Blurred vision, optic neuropathy** | Loss of vision |
| **Ear and labyrinth disorders** | Vertigo | Tinnitus | |
| **Vascular disorders** | | Hypertension, hypotension, phlebitis/thrombophlebitis | |
| **Gastrointestinal disorders** | Diarrhoea, nausea, vomiting, abdominal pain, cramps, distension, loose stools, metallic taste | Constipation, dry mouth, dyspepsia, gastritis, increased thirst, pancreatitis, stomatitis, tongue discolouration** or disorder, superficial tooth discolouration** | |
| **Skin and subcutaneous tissue disorders** | | Angioedema**dermatitis, diaphoresis, pruritus, rash**, urticaria, bullous skin disorders such described as Stevens Johnson syndrome** | |
| **Renal and urinary disorders** | | Polyuria | |
| **Reproductive system and breast disorders** | | Vulvovaginal disorder | |
| **General disorders and administrative site conditions** | | Chills, fatigue, fever, injection site pain, localised pain | |
| **Investigations** | Laboratory abnormalities-Chemistry: Increased total bilirubin, AST, ALT, LDH, alkaline phosphatase, BUN, creatine kinase, lipase, amylase or non-fasting glucose, decreased total protein, albumin, sodium, | Laboratory abnormalities-Chemistry: Increased creatinine, sodium, calcium; decreased non-fasting glucose, increased or decreased chloride, | |

| | | | |
|---|---|---|---|
| | calcium, increased or decreased potassium or bicarbonate, | | |
| | laboratory abnormalities- Haematology: increased neutrophils or eosinophils, decreased haemoglobin, haematocrit or red blood cell count, increased or decreased platelet or white blood cell counts | laboratory abnormalities- Haematology: increased reticulocyte count; decreased neutrophils | |

** The statement "frequency unknown" has been included into the frequency categories in Section 4.8. Undesirable effects, as the frequency cannot be confirmed with the available data.*

*** Post-marketing information*

*(c) Description of selected adverse reactions (Post-marketing information)*

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) and sideroblastic anaemia have been reported.

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 (see section 4.4). Lactic acidosis (see section 4.4), rash, convulsions, angioedema and anaphylaxis have been reported. Very rare reports of bullous skin disorders including severe cutaneous adverse reactions such as those described as toxic epidermal necrolysis and Stevens Johnson syndrome have been received.

*Serotonin syndrome* has been reported in patients receiving concomitant serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and LINEZOLID 600 mg/300 ml ASPEN (see section 4.4).

*Gastrointestinal disorders:* Tongue discoloration. Superficial tooth discoloration has been reported very rarely with the use of linezolid, as in LINEZOLID 600 mg/300 ml ASPEN. The discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome. Abdominal pain, abdominal cramps and abdominal distension have been reported and considered medicine-related in controlled clinical trials.

*Reporting of suspected adverse reactions*

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

**SAHPRA:** https://www.sahpra.org.za/health-products-vigilance/

**Aspen Pharmacare:**

**E-mail:** Drugsafety@aspenpharma.com

**Tel:** 0800 118 088

### 4.9 Overdose

**Symptoms**

No cases of overdose have been reported.

**Treatment**

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

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotic

Pharmacotherapeutic group: Antibiotics for systemic use, other antibiotics.

ATC code: J01XX08

*Mechanism of action*

Linezolid is a synthetic antibacterial medicine of the oxazolidinone class of antibiotics. It has *in vitro* activity against aerobic Gram-positive bacteria and anaerobic microorganisms. It selectively inhibits bacterial protein synthesis through binding to sites on the bacterial ribosome and prevents the formation of a functional 70S initiation complex that is an essential component of the translation process.

The *in vitro* post-antibiotic effect (PAE) of linezolid for *Staphylococcus aureus* was approximately 2 hours.

*Susceptibility:* The following gives an approximate guidance on the probabilities as to whether microorganisms will be susceptible to linezolid or not. (Only microorganisms relevant to the given clinical indications are presented).

*Table C*

| **Category** |
|---|
| **Susceptible organisms** |
| Gram-positive aerobes:<br>*Corynebacterium jeikeium*<br>*Enterococcus casseliflavus* |

| |
|---|
| *Enterococcus faecalis* (including glycopeptide resistant strains) *<br>*Enterococcus faecium* (including glycopeptide resistant strains) *<br>*Enterococcus gallinarum*<br>*Listeria monocytogenes*<br>*Staphylococcus aureus* (including methicillin resistant strains) *<br>*Staphylococcus aureus* (glycopeptide intermediate strains) *Staphylococcus epidermidis* (including methicillin resistant strains) *<br>*Staphylococcus haemolyticus*<br>*Staphylococcus lugdunensis*<br>*Streptococcus agalactiae* *<br>*Streptococcus intermedius*<br>*Streptococcus pneumoniae* (including multi drug resistant strains [MDRSP]) □<br>*Streptococcus pyogenes* *<br>Group C streptococci<br>Group G streptococci<br>Viridans group streptococci |
| Gram-positive anaerobes:<br>*Clostridium perfringens*<br>*Peptostreptococcus* species<br>*Peptostreptococcus anaerobius* |
| Other:<br>*Chlamydia pneumoniae* |
| **Intermediately susceptible organisms** |

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|---|
| *Legionella* species<br>*Mycoplasma* species<br>*Moraxella catarrhalis* |
| **Resistant organisms** |
| *Haemophilus influenzae*<br>*Neisseria* species<br>*Enterobacteriaceae*<br>*Pseudomonas* species |
| * Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications<br> MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates previously known as penicillin resistant *Streptococcus pneumoniae* and are strains resistant to two or more of the following antibiotics: penicillin, second generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole. |

*Resistance:* Linezolid's mechanism of action differs from that of other antibiotics (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 medicines.

*In vitro* studies have shown that resistance to linezolid develops slowly via multiple step mutations in 23S ribosomal RNA and occurs at frequencies of less than $1 \times 10^{-9}$ to $1 \times 10^{-11}$.

### 5.2 Pharmacokinetic properties

LINEZOLID 600 mg/300 ml ASPEN primarily contains linezolid that is biologically active and is metabolised to form inactive metabolites.

The aqueous solubility of linezolid is approximately 3 mg/mL and is independent of pH between pH 3 to 9.

**Absorption**

Maximum plasma concentrations are reached within 2 hours of dosing and absolute bioavailability is approximately 100 %. It is not affected by food**.**

**Distribution**

The volume of distribution at steady-state averages at about 40 to 50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31 %.

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 linezolid dosing.

**Metabolism**

Linezolid is metabolised by a non-enzymatic process**.** Metabolic oxidation of the morpholine ring results primarily in two inactive open-ring carboxylic acid derivatives. The hydroxyethyl glycine metabolite (B) is the predominant human metabolite and the amino ethoxy acetic acid metabolite (A) is less abundant. Linezolid is not detectably metabolised by cytochrome P450 (CYP) isoenzymes *in vitro* and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Linezolid does not significantly induce major cytochrome P450 isoenzymes in rats and does not induce human CYP2C9.

**Elimination**

Under steady-state conditions, linezolid is primarily excreted in the urine as metabolite B (40 %), parent medicine (30 to 35 %) and metabolite A (10 %). The elimination half-life of the parent medicine averages at about 5 to 7 hours. Non-renal clearance accounts for approximately 65 % of the total clearance of linezolid.

**Special populations**

*Elderly*

The pharmacokinetics of linezolid is not significantly altered in elderly patients aged 65 and over.

*Renal insufficiency*

No dose adjustment is necessary in patients with either mild, moderate or severe renal insufficiency, as linezolid clearance is independent of creatinine clearance. There is evidence that the primary metabolites of linezolid accumulate in patients with severe renal insufficiency (i.e. $CL_{CR} < 30$ mL/min). The clinical significance of this has not yet been established. As approximately 30 % of a dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration), linezolid should be given after dialysis in patients receiving such treatment.

*Hepatic insufficiency*

The pharmacokinetics of linezolid are not altered in patients with mild to moderate hepatic insufficiency. Dose adjustment in such patients is, therefore, not required. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency has not been evaluated. However, as linezolid is metabolised by a nonenzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

*Paediatric*

The pharmacokinetics of linezolid following a single IV dose were investigated in paediatric patients ranging in age from birth through 17 years (including premature and full-term neonates).

The $C_{max}$ and the volume of distribution ($V_{ss}$) are similar regardless of age in paediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from > 1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of paediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values approach these observed for the adult population. There is wider inter-subject variability in linezolid clearance and systemic medicine exposure (AUC) across all paediatric age groups as compared with adults.

## 6 PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Citric acid anhydrous, glucose monohydrate, hydrochloric acid (for pH adjustment) sodium citrate, sodium hydroxide (for pH adjustment), water for injections.

### 6.2 Incompatibilities

LINEZOLID 600 mg/300 ml ASPEN solution for infusion is known to be physically incompatible with the following medicines: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, phenytoin sodium, erythromycin lactobionate and trimethoprim-sulfamethoxazole (see section 4.5).

LINEZOLID 600 mg/300 ml ASPEN solution for infusion was chemically incompatible when combined with ceftriaxone sodium (see section 4.5).

### 6.3 Shelf life

30 months

### 6.4 Special precautions for storage

Store at or below 30 °C. Keep the polyethylene container in the outer carton in order to protect from light. Single use only.

### 6.5 Nature and contents of container

300 ml of LINEZOLID 600 mg/300 ml ASPEN is filled into a polyethylene bag and packed in a cardboard carton.

### 6.6 Special precautions for disposal and other handling

LINEZOLID 600 mg/300 ml ASPEN solution for infusion must be used immediately after the seal is first broken. LINEZOLID 600 mg/300 ml ASPEN solution for infusion is supplied in single-use, ready-to-use infusion bags. Parenteral medicines should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired.

Administer LINEZOLID 600 mg/300 ml ASPEN solution for 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 600 mg/300 ml ASPEN solution for infusion is to be given concomitantly with another medicine, each medicine should be given separately, in accordance with the recommended dosage and route of administration for each medicine.

*Compatible infusion solutions:* 0,9 % sodium chloride injection, 5 % dextrose injection, lactated ringer's injection.

## 7 HOLDER OF CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead, 2191

## 8 REGISTRATION NUMBER

48/20.1.1/0358

## 9 DATE OF FIRST AUTHORISATION

10 November 2020

## 10 DATE OF REVISION OF TEXT

10 November 2020

ZA_LINEASSOLINF_2011_00