PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LINEZOLID 600 mg/300 ml FRESENIUS solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 300 mL infusion bag or bottle of LINEZOLID FRESENIUS contains 600 mg linezolid; providing 2 mg linezolid per mL.

Excipients with known effect:

Each 300 mL also contains 15,072 g glucose monohydrate and 131 mg sodium (as sodium citrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

Freeflex bags: Isotonic, clear, practically free from particles, colourless to yellow solution.

KabiPac bottles: Isotonic, clear, practically free from particles, colourless to yellow or slightly brownish solution.

pH: 4,6 – 5,0

Osmolality: 270 – 330 mOsmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LINEZOLID FRESENIUS is indicated for the treatment of patients with the following infections caused by susceptible strains of the designated Gram-positive micro-organisms (see section 5). **LINEZOLID FRESENIUS 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 FRESENIUS 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 FRESENIUS in the outpatient setting.

Prescribers should adhere to the principles of antibiotic stewardship.

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 FRESENIUS solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to an oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as LINEZOLID FRESENIUS has an oral bioavailability of approximately 100 %.

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

The recommended dosage schedule for LINEZOLID FRESENIUS is as follows:

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

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 – 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 – 28 consecutive days

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 – 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 – 28 consecutive days

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

Special populations

Elderly patients:

No dose adjustment is necessary.

Patients with renal insufficiency:

No dosage 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 FRESENIUS in patients with severe renal insufficiency, LINEZOLID FRESENIUS should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

Haemodialysis:

As approximately 30 % of a LINEZOLID FRESENIUS dose is removed during 3 hours of haemodialysis, LINEZOLID FRESENIUS should be given after dialysis in patients receiving such treatment. The primary metabolites of LINEZOLID FRESENIUS 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.
LINEZOLID FRESENIUS should therefore 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 FRESENIUS 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 is limited clinical data, and it is recommended that LINEZOLID FRESENIUS should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk (see section 5.2).

Method of administration

Instructions for use/handling:

Intravenous administration:

LINEZOLID FRESENIUS solution for infusion must be used immediately after the seal is first broken. LINEZOLID FRESENIUS 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 FRESENIUS 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 FRESENIUS 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.

LINEZOLID FRESENIUS 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.

LINEZOLID FRESENIUS solution for infusion is chemically incompatible when combined with ceftriaxone sodium.

4.3 Contraindications

LINEZOLID FRESENIUS formulations are contraindicated for use:

- in patients who have known hypersensitivity to linezolid or any excipients in the formulation (see section 6.1).
- in patients treated with monoamine oxidase (MAO) inhibitors or within two weeks of taking such a medicine.
- in mothers breastfeeding their babies (see section 4.6).

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

- Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder or acute confusional states;

- Patients taking any of the following medicines: serotonin re-uptake inhibitors (see section 4.4), tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), directly and indirectly acting sympathomimetic medicines (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive medicines (e.g. epinephrine, norepinephrine), dopaminergic medicines (e.g. dopamine, dobutamine), pethidine or buspirone (see section 4.5).

4.4 Special warnings and precautions for use

Underlying clinical conditions:

- Unless patients are monitored for potential increases in blood pressure, LINEZOLID FRESENIUS **should not** be administered to patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, hyperthyroidism, bipolar depression, schizoaffective disorder, acute confusional states.
- The risk/benefit should be thoroughly considered in patients with worsening myelosuppression and diarrhoea (see “Myelosuppression” and “Colitis and superinfection” in this section).

Serotonin syndrome

Spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic medicines have been reported. Since there is limited experience with concomitant administration of LINEZOLID FRESENIUS and serotonergic medicines (such as serotonin re-uptake inhibitors, tricyclic antidepressants and serotonin 5-HT_1 receptor agonists) doctors should be aware of the possibility of signs and symptoms of serotonin syndrome (e.g., hyperpyrexia, hyperreflexia, incoordination and cognitive

dysfunction) in patients receiving such concomitant therapy (see sections 4.3, 4.5 and 4.8).

If such signs or symptoms occur, doctors should consider discontinuing either one or both medicines. Should the concomitant serotonergic medicine be withdrawn, discontinuation symptoms may occur.

Rhabdomyolysis

Rhabdomyolysis has been reported with the use of linezolid. Linezolid should be used with caution in patients with pre-disposing factors for rhabdomyolysis. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated.

Colitis and superinfection

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile* associated diarrhoea, has been reported with linezolid (contained in LINEZOLID FRESENIUS) and may vary in seriousness from mild diarrhoea to fatal colitis. It is therefore important to consider this diagnosis in patients presenting with diarrhoea during or after administration of LINEZOLID FRESENIUS.

Superinfection

The use of antibiotics, including LINEZOLID FRESENIUS, may occasionally result in an overgrowth of non-susceptible organisms. For example, candidiasis has been reported. Should superinfection occur during therapy, appropriate measures should be taken.

Lactic acidosis

Lactic acidosis has been reported with the use of LINEZOLID FRESENIUS. **Patients who develop signs and symptoms of recurrent nausea or vomiting, metabolic acidosis, or a low bicarbonate level while receiving LINEZOLID FRESENIUS, should receive immediate medical attention.**

Mitochondrial dysfunction

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

Myelosuppression

Myelosuppression (anaemia, including pure red blood cell aplasia, leucopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving LINEZOLID FRESENIUS (see section 4.8). Patients particularly at risk are those who have received LINEZOLID FRESENIUS for more than 10 or 14 days, who are receiving other bone marrow suppressant medicines, or who have pre-existing myelosuppression, severe renal impairment or moderate to severe hepatic impairment.

Elderly patients treated with LINEZOLID FRESENIUS 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.

LINEZOLID FRESENIUS should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible.

Complete blood counts (including haemoglobin levels, platelets, and total and differential leucocyte counts) should be monitored at least weekly in patients who receive LINEZOLID FRESENIUS, regardless of baseline blood count.
Discontinuation of therapy with LINEZOLID FRESENIUS should be considered in patients who develop or have worsening myelosuppression.

A higher incidence of serious anaemia was reported in patients receiving LINEZOLID FRESENIUS 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, with more cases occurring in patients who received linezolid (as in LINEZOLID FRESENIUS) therapy for more than 28 days.

Cases of sideroblastic anaemia have been reported. Where time of onset was known, most patients 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.

Peripheral and optic neuropathy:
Peripheral and optic neuropathy and optic neuritis sometimes progressing to loss of vision, have been reported with LINEZOLID FRESENIUS (see section 4.8), mainly in patients treated for longer than the maximum recommended duration of 28 days (see “Long-term use” below).
If peripheral or optic neuropathy occurs, the continued use of LINEZOLID FRESENIUS should be weighed against the potential risks.

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 patient receives LINEZOLID FRESENIUS for longer than the recommended 28 days, his/her visual function should be regularly monitored.
There may be an increased risk of neuropathies when LINEZOLID FRESENIUS is used in patients currently taking or who have recently taken anti-mycobacterial medications for the treatment of tuberculosis.

Convulsions:

Convulsions may occur in patients treated with LINEZOLID FRESENIUS (see section 4.8), particularly in patients with a history of convulsions or risk factors for convulsions. Patients should be advised to inform their doctor if they have a history of seizures.

Use with tyramine-rich foods

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

Antibacterial spectrum

LINEZOLID FRESENIUS has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections (see section 5.1).
Patients with mixed (Gram-negative and Gram-positive) infections are at a higher risk of mortality when LINEZOLID FRESENIUS is given as monotherapy; LINEZOLID FRESENIUS must therefore be used with appropriate antibacterial cover for Gram-negative organisms in such patients.

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

LINEZOLID FRESENIUS is not intended for the treatment of patients with catheter-related infections of the blood stream.

Excess mortality was seen in patients treated with linezolid (as in LINEZOLID FRESENIUS), relative to vancomycin/dicloxacillin/oxacillin, in seriously ill patients with intravascular catheter-related infections.

LINEZOLID FRESENIUS should be used with special caution in patients exposed to a high risk of life-threatening systemic infections, such as those with infections related to central venous catheters in intensive care units.

In complicated skin and soft tissue infections LINEZOLID FRESENIUS should only be used in patients with known or possible co-infection with Gram-negative organisms if there are no alternative treatment options available. In these circumstances treatment against Gram-negative organisms must be initiated concomitantly.

Resistance:

There have been reports of linezolid resistance in enterococci. Linezolid resistance has also been observed in staphylococci, such as meticillin-resistant *Staphylococcus aureus*, *S. auricularis* and *S. epidermidis*.

Due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms, doctors should carefully consider alternatives before initiating treatment with LINEZOLID FRESENIUS 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.

Long-term use:

The safety and efficacy of LINEZOLID FRESENIUS when administered for periods longer than 28 days have not been established.

Patient populations:

LINEZOLID FRESENIUS has not been studied in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.

Renal impairment:

LINEZOLID FRESENIUS should be used with special care in patients with severe renal impairment and only when it is reckoned that the expected benefit exceeds the risk.

Hepatic impairment:

It is recommended that LINEZOLID FRESENIUS should only be considered for treatment in patients with serious hepatic insufficiency if it is reckoned that the expected benefit will exceed the risk.

Porphyria:

LINEZOLID FRESENIUS is possibly porphyrinogenic and should therefore only be used when no safer alternative is available, and precautions should be considered in vulnerable patients.

Paediatric patients:

Pharmacokinetic information generated in paediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of paediatric patients with central nervous system infections is not recommended.

Excipients:

LINEZOLID FRESENIUS contains 15,072 g **glucose monohydrate** per 300 mL solution (see section 2). This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance.
LINEZOLID FRESENIUS also contains 131 mg **sodium** (as sodium citrate; see section 2) per 300 mL solution. The sodium content should be taken into account in patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Unless there are facilities available for close observation and monitoring of blood pressure, LINEZOLID FRESENIUS should not be administered to patients taking serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), directly and indirectly acting sympathomimetic medicines (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive medicines (e.g. epinephrine, norepinephrine), dopaminergic medicines (e.g. dopamine, dobutamine), pethidine or buspirone (see section 4.4).

Monoamine oxidase inhibitors

LINEZOLID FRESENIUS is contraindicated in patients treated with monoamine oxidase inhibitors or within two weeks of taking such a medicine (see section 4.3). LINEZOLID FRESENIUS is a reversible, non-selective monoamine oxidase inhibitor (MAOI), which produces a mild, reversible enhancement of the pressor responses induced by pseudoephedrine and phenylpropanolamine hydrochloride. Thus, the potential for interaction with sympathomimetic or adrenergic medicines should be considered. See section 4.4. Doses of compounds, such as dopamine or epinephrine (adrenaline), should be titrated to achieve the desired response.

Serotonergic medicines

Serotonin syndrome, associated with the simultaneous administration of LINEZOLID FRESENIUS and serotonergic medicines, including antidepressants such as selective serotonin re-uptake inhibitors (SSRIs) has been reported (see section 4.8 and section 4.4).

Although LINEZOLID FRESENIUS has the potential for interaction with serotonergic medicines, no serotonin effects (e.g., confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) were observed in subjects receiving linezolid and dextromethorphan.

Opioid analgesics

LINEZOLID FRESENIUS is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Pethidine should not be given to patients receiving MAO inhibitors or within 14 days of their discontinuation as very severe reactions, including coma, severe respiratory depression, cyanosis and hypotension may occur.

Mechanism of possible interactions:

LINEZOLID FRESENIUS 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 FRESENIUS without changes in dosage regimen.

Also, no interactions have been observed with either aztreonam or gentamicin.

Tyramine-rich foods:

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) should be avoided to prevent a pressor response.

Rifampicin:

Concomitant administration of rifampicin with LINEZOLID FRESENIUS may cause a decrease of about 20 % in linezolid C_{max} and a decrease of about 30 % in linezolid AUC. The mechanism of this interaction and the clinical significance thereof is not known.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of LINEZOLID FRESENIUS in pregnancy is contraindicated as safety has not been demonstrated.

Breastfeeding

The use of LINEZOLID FRESENIUS in lactation is contraindicated.

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

Fertility

In animal studies, linezolid caused a reduction in fertility.

4.7 Effects on ability to drive and use machines

LINEZOLID FRESENIUS may cause dizziness, hypotension and blurred vision. Patients should be advised not to drive or operate machines if these side effects occur.

4.8 Undesirable effects

Infections and infestations:

Frequent: Oral and vaginal candidiasis or fungal infection.

Less frequent: Antibiotic associated colitis, pseudomembranous colitis and *C. difficile* associated diarrhoea (may be fatal; see section 4.4), vulvovaginal disorder, vaginitis.

Blood and the lymphatic system disorders:

Less frequent: Reversible myelosuppression* anaemia*, eosinophilia, leukopenia*, neutropenia, thrombocytopenia*, pancytopenia*, sideroblastic anaemia.*

Immune system disorders:

Frequency not known: Hypersensitivity reactions, anaphylaxis, angioedema, bullous skin disorders described as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Metabolism and nutrition disorders:

Less frequent: Increased serum creatine phosphokinase, hyperglycaemia, lactic acidosis*, hyponatraemia.

Psychiatric disorders:

Frequent: Insomnia

Nervous system disorders:

Frequent: Headache, taste alterations, metallic taste.

Less frequent: Dizziness, hypoaesthesia, paraesthesia, peripheral neuropathy*, convulsions*, serotonin syndrome**.

Eye disorders:

Less frequent: Blurred vision*, optical neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*, changes in visual field defect.

Ear and labyrinth disorders:

Less frequent: Tinnitus

Cardiac disorders:

Less frequent: Dysrhythmia (tachycardia)

Vascular disorders:

Less frequent: Hypertension, hypotension, phlebitis, thrombophlebitis, transient ischaemic attacks.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, abdominal pain, cramps or distension.

Less frequent: Constipation, dry mouth, dyspepsia, gastritis, abdominal distention, increased thirst, pancreatitis, stomatitis, tongue discolouration or disorder, localised or general abdominal pain, glossitis, loose stools.

Hepatobiliary disorders:

Frequent: Abnormal liver function tests (see "**Investigations**" below).

Skin and subcutaneous tissue disorders:

Less frequent: Dermatitis, diaphoresis, pruritus, rash, urticaria, alopecia.

Musculoskeletal, connective tissue and bone disorders:

Less frequent: Superficial tooth discolouration, rhabdomyolysis*.

Renal and urinary disorders:

Less frequent: Polyuria, increased creatinine, renal failure.

General disorders and administration site conditions:

Less frequent: Chills, fatigue, fever, injection site pain, phlebitis/thrombophlebitis, increased thirst.

Investigations:

Frequent: Increased total bilirubin, AST, ALT, LDH, alkaline phosphatase, blood urea, creatine kinase, lipase, amylase or non-fasting glucose; decreased total protein, albumin, sodium, calcium, increased or decreased potassium or bicarbonate.

	Increased neutrophils or eosinophils, decreased haemoglobin, haematocrit or red blood cell count, increased or decreased platelet or white blood cell counts.
Less frequent:	Increased reticulocyte count, decreased neutrophils, creatinine, sodium, calcium; decreased non-fasting glucose, increased or decreased chloride**.**

* See section 4.4

** See section 4.3

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of LINEZOLID FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of LINEZOLID FRESENIUS. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website.

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed either directly or via the national pharmacovigilance electronic reporting systems.

4.9 Overdose

Refer to section 4.8.

Supportive care is advised together with maintenance of glomerular filtration.

Approximately 30 % of a LINEZOLID FRESENIUS dose is removed during 3 hours of haemodialysis, but no data is available for the removal of LINEZOLID FRESENIUS by peritoneal dialysis or haemoperfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Other antibacterials, ATC code: J01XX08

Linezolid belongs to the oxazolidinone class of antimicrobials.

Linezolid targets the initiation phase of bacterial translation by preventing the formation of a functional 70S initiation complex.

Linezolid is bacteriostatic against enterococci and staphylococci and bactericidal against streptococci.

Linezolid has poor activity against most Gram-negative aerobic or anaerobic bacteria.

Resistant organisms:

Haemophilus influenza

Enterobacteriaceae

Neisseria species

Pseudomonas species

Organisms with varied susceptibility:

Legionella species

Mycoplasma species

Moraxella catarrhalis

Resistance:

There is no cross-resistance between linezolid and e.g. the aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol.

5.2 Pharmacokinetic properties

Distribution:

The volume of distribution at steady-state is about 40 to 50 litres in healthy adults.

Plasma protein binding is about 30 %.

Metabolism:

Linezolid is metabolised to form inactive metabolites.

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 main 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 compound (30 - 35 %) and metabolite A (10 %). The elimination half-life

of the parent compound is about 5 - 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 mild, moderate or severe renal insufficiency, as linezolid clearance is independent of creatinine clearance.

Primary metabolites of linezolid may probably accumulate in patients with severe renal insufficiency (i.e., CL_{CR} < 30 mLmin). As approximately 30 % of a dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration) treatment should be given after dialysis in patients receiving such treatment.

Hepatic insufficiency:

The pharmacokinetics of linezolid is 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 non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Children:

The C_{max} and the volume of distribution (V_{ss}) are similar in paediatric patients aged newborn to 17 years (including premature and full-term neonates) after a single IV dose. The clearance of linezolid however 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. With increasing age of paediatric patients, the clearance of linezolid gradually decreases and by adolescence mean clearance values approach those observed for the adult population.
There is also wider inter-subject variability in linezolid clearance and systemic medicine exposure (AUC) across all paediatric age groups as compared with adults.

5.3 Preclinical safety

Not applicable.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Glucose monohydrate

Sodium citrate

Citric acid, anhydrous

Hydrochloric acid 1M (for pH adjustment)

Sodium hydroxide 1M (for pH adjustment)

6.2 Incompatibilities

Do not use the intravenous infusion bag in series connections. Do not introduce additives into the intravenous solution. If LINEZOLID FRESENIUS 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 product (see section 4.2).

Compatible infusion solutions:

0,9 % Sodium chloride injection, 5 % dextrose injection, Lactated Ringer's injection (see section 4.2).

LINEZOLID FRESENIUS 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.

LINEZOLID FRESENIUS solution for infusion is chemically incompatible when combined with ceftriaxone sodium (see section 4.2).

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at room temperature, at or below 25 °C. Do not freeze. Protect from light – the infusion bags must be kept in their overpouch, until ready to use. The infusion bags and KabiPac bottles are only intended for single-use. Discard any unused solution.

6.5 Nature and contents of container

FreeFlex bags

Single use freeflex infusion bags packaged in an aluminium foil overpouch, available in a pack size of 300 mL (600 mg linezolid).

The freeflex® container closure system for LINEZOLID FRESENIUS solution for infusion consists of three components: film, ports (tubes and closure system consisting of stoppers and caps) and hot stamp foil ink. A printed overwrap provides additional product

protection from loss of water (via permeation) as well as protection from light. Packed as 10 x 300 mL.

KabiPac bottles

300 mL solution is filled into a 500 mL KabiPac bottle. The KabiPac packaging system consists of a polyethylene bottle and a cap with an administration point and an addition point, which are two separate, easily distinguishable ports for infusion and injection. The cap is made of polyethylene or a mixture of polyethylene and polypropylene.

Inside the cap, two polyisoprene stoppers serve for the insertion and support of the needle or the spike. The KabiPac packaging system is a unit dose container with a hanger at the bottom of the bottle.

The KabiPac bottles are packed individually into cartons. Ten such single-packed bottles are then packed into an outer carton in pack sizes of 10 x 300 mL.

6.6 Special precautions for disposal and other handling

LINEZOLID FRESENIUS solution for infusion must be used immediately after the seal is first broken. LINEZOLID FRESENIUS solution for infusion is supplied in single-use, ready-to-use infusion bags and unit dose KabiPac bottles. 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.

The infusion bags and KabiPac bottles are only intended for single-use. Discard any unused solution (see section 4.2).

7 HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER

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9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10. DATE OF REVISION OF THE TEXT

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