Package leaflet: Information for the user

Linezolid 2 mg/ml solution for infusion
linezolid

Read all of this leaflet carefully before this medicinal product is given to you because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist or nurse.
- If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Linezolid is and what it is used for

Linezolid is an antibiotic of the oxazolidinones group that works by stopping the growth of certain bacteria (germs) that cause infections in adults. It is used to treat pneumonia and some infections in the skin or under the skin. Your doctor will have decided if Linezolid is suitable to treat your infection.

2. What you need to know before you are treated with Linezolid

You should not be treated with Linezolid
- if you are allergic to linezolid or any of the other ingredients of this medicine (listed in section 6).
- if you are taking or have taken within the last 2 weeks any medicines known as monoamine oxidase inhibitors. (MAOIs: for example phenelzine, isocarboxazid, selegiline, moclobemide). These medications may be used to treat depression or Parkinson's disease.
- if you are breast-feeding. This is because Linezolid passes into breast milk and could affect the baby.

Warnings and precautions
Talk to your doctor or pharmacist or nurse before you are treated with Linezolid.
Linezolid may not be suitable for you if you answer yes to any of the following questions. In this case tell your doctor as he/she will need to check your general health and your blood pressure before and during your treatment or may decide that another treatment is better for you.
Ask your doctor if you are not sure whether these categories apply to you.
- Do you have high blood pressure, whether or not you are taking medicines for this?
- Have you been diagnosed with an overactive thyroid?
- Do you have a tumour of the adrenal glands (phaeochromocytoma) or carcinoid syndrome (caused by tumours of the hormone system with symptoms of diarrhoea, flushing of the skin, wheezing)?
- Do you suffer from manic depression, schizoaffective disorder, mental confusion or other mental problems?
- Do you have a history of hyponatraemia (low blood sodium levels) or do you take medicines that lower blood sodium levels e.g. certain diuretics (also called "water tablets") such as

hydrochlorothiazide?
- Do you take any opioids?

The use of certain medicines, including antidepressants and opioids, together with Linezolid can lead to serotonin syndrome, a potentially life-threatening condition (see section 2 “Other medicines and Linezolid” and section 4).

Take special care with Linezolid
Tell your doctor before you are treated with this medicine if you:
- are elderly
- bruise and bleed easily
- are anaemic (have low red blood cells)
- are prone to getting infections
- have a history of seizures
- have liver problems or kidney problems particularly if you are on dialysis
- have diarrhoea

Tell your doctor immediately if during treatment you suffer from:
- problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.
- loss of sensitivity in your arms or legs or a sensation of tingling or pricking in your arms or legs.
- You may develop diarrhoea while taking or after taking antibiotics, including Linezolid. If this becomes severe or persistent or you notice that your stools contains blood or mucus, you should stop taking Linezolid immediately and consult your doctor. In this situation, you should not take medicines that stop or slow bowel movement.
- recurrent nausea or vomiting, abdominal pain or rapid breathing.
- unexplained muscle pain, tenderness, or weakness, and/or dark urine. These can be signs of a serious condition called rhabdomyolysis (muscle breakdown), which can lead to kidney damage.
- feeling sick and unwell with muscle weakness, headache, confusion, and memory impairment which may indicate hyponatraemia (low blood sodium levels).

Other medicines and Linezolid
There is a risk that Linezolid may sometimes interact with certain other medicines to cause side effects such as changes in blood pressure, temperature or heart rate.

Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Tell your doctor if you are taking or have taken within the last 2 weeks the following medicines as Linezolid **must not** be taken if you are already taking these medicines or have taken them recently (see also Section 2 above ‘**You should not be treated with Linezolid ’**).
- monoamine oxidase inhibitors (MAOIs; for example phenelzine, isocarboxazid, selegiline, moclobemide). These may be used to treat depression or Parkinson’s disease.

Also tell your doctor if you are taking the following medicines. Your doctor may still decide to give you Linezolid, but will need to check your general health and your blood pressure before and during your treatment. In other cases, your doctor may decide that another treatment is better for you.

- Decongestant cold or flu remedies containing pseudoephedrine or phenylpropanolamine.
- Some medicines used to treat asthma such as salbutamol, terbutaline, fenoterol.
- Certain antidepressants known as tricyclics or SSRIs (selective serotonin reuptake inhibitors). There are many of these, including amitriptyline, citalopram, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, sertraline.
- Medicines used to treat migraine such as sumatriptan and zolmitriptan.
- Medicines used to treat sudden, severe allergic reactions such as adrenaline (epinephrine).

- Medicines which increase your blood pressure, such as noradrenaline (norepinephrine) dopamine and dobutamine.
- Opioids e.g., pethidine - used to treat moderate to severe pain.
- Medicines used to treat anxiety disorders, such as buspirone.
- Medicines that stop blood clotting, such as warfarin.
- An antibiotic called rifampicin.

Linezolid with food and drink
- You can take Linezolid either before, during or after a meal.
- Avoid eating large amounts of mature cheese, yeast extracts, or soya bean extracts e.g. soy sauce and drinking alcohol, especially draught beers and wine. This is because Linezolid may react with a substance called tyramine which is naturally present in some foods. This interaction may cause an increase in your blood pressure.
- If you develop a throbbing headache after eating or drinking, tell your doctor, pharmacist or nurse immediately.

Pregnancy and breast-feeding and fertility
The effect of Linezolid in pregnant women is not known. Therefore, it should not be taken in pregnancy unless advised by your doctor. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should not breast-feed when taking Linezolid because it passes into breast milk and could affect the baby.

Driving and using machines
Linezolid may make you feel dizzy or experience problems with your vision. If this happens, do not drive or operate any machinery. Remember that if you are unwell your ability to drive or operate machinery may be affected.

Linezolid contains glucose.
300 ml of solution for infusion contains 13.7 g glucose. This should be taken into account in patients with diabetes mellitus.

Linezolid contains sodium.
300 ml of solution for infusion contains 114 mg sodium (main component of cooking/table salt). This is equivalent to 5.7 % of the recommended maximum daily dietary intake of sodium for an adult.

3. How Linezolid is given

Adults
Always take this medicine exactly as described in this leaflet or as your doctor, pharmacist or nurse has told you. Check with your doctor, pharmacist or nurse if you are not sure.

This medicine will be given to you through a drip (by infusion into a vein) by a doctor or healthcare professional. The usual dose for adults (18 years and older) is 300 ml (600 mg linezolid) twice daily which is given directly into the blood stream (intravenously) by a drip over a period of 30 to 120 minutes.

If you are on kidney dialysis, you should be given Linezolid after your dialysis treatment.

A course of treatment usually lasts 10 to 14 days, but can last up to 28 days. The safety and effectiveness of this medicine have not been established for treatment periods longer than 28 days. Your doctor will decide how long you should be treated.

While you are taking Linezolid, your doctor should perform regular blood tests to monitor your blood count.

Your doctor should monitor your eyesight if you take Linezolid for more than 28 days.

Use in children and adolescents

Linezolid is not normally used to treat children and adolescents (under 18 years old).

If you receive more Linezolid than you should
If you are concerned that you may have been given too much Linezolid, tell your doctor or a nurse at once.

If you forget to use Linezolid
As you will be given this medicine under close supervision, it is very unlikely that you will miss a dose. If you think that you have missed a dose of treatment, tell a doctor or nurse at once. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor, nurse or pharmacist immediately if you notice any of these side effects during your treatment with Linezolid:

The serious side effects (with frequency in brackets) of Linezolid are:

- Severe skin disorder (uncommon), swelling, particularly around the face and neck (uncommon), wheezing and/or difficulty breathing (rare). This may be the sign of an allergic reaction and it may be necessary for you to stop taking Linezolid. Skin reactions such as a raised purple rash due to inflammation of the blood vessels (rare), red sore skin and flaking (dermatitis) (uncommon), rash (common), itching (common).
- Problems with your vision (uncommon) such as blurred vision (uncommon), changes in colour vision (not known), difficulty in seeing detail (not known) or if your field of vision becomes restricted (rare).
- Severe diarrhoea containing blood and/or mucus (antibiotic associated colitis including pseudomembranous colitis), which in rare circumstances may develop into complications that are life-threatening (uncommon).
- Recurrent nausea or vomiting, abdominal pain or rapid breathing (rare).
- Fits or seizures (uncommon) have been reported with Linezolid.
- Serotonin syndrome (not known): You should let your doctor know if you experience agitation, confusion, delirium, rigidity, tremor, incoordination, seizure rapid heartbeat, severe breathing problems, and diarrhoea (suggestive of serotonin syndrome) while also taking antidepressants known as SSRIs or opioids (see section 2).
- Unexplained bleeding or bruising, which may be due to changes in the numbers of certain cells in the blood which may affect blood clotting or lead to anaemia (common).
- Changes in numbers of certain cells in the blood which may affect your ability to fight infection (uncommon) some signs of infection include: any fever (common), sore throat (uncommon), mouth ulcers (uncommon) and tiredness (uncommon).
- Rhabdomyolysis (rare): Signs and symptoms include unexplained muscle pain, tenderness, or weakness, and/or dark urine. These can be signs of a serious condition called rhabdomyolysis (muscle breakdown), which can lead to kidney damage.
- Inflammation of the pancreas (uncommon).
- Convulsions (uncommon).
- Transient ischaemic attacks (temporary disturbance of blood flow to the brain causing short term symptoms such as loss of vision, leg and arm weakness, slurring of speech and loss of consciousness) (uncommon).

- "Ringing" in the ears (tinnitus) (uncommon).

Numbness, tingling or blurred vision have been reported by patients who have been given Linezolid for more than 28 days. If you experience difficulties with your vision you should consult your doctor as soon as possible.

Other side effects include:

Common (may affect up to 1 in 10 people):
- Fungal infections especially vaginal or oral "thrush"
- Headache
- Metallic taste in the mouth
- Diarrhoea, nausea or vomiting
- Changes in some blood test results including those measuring proteins, salts or enzymes which measure your kidney or liver function or blood sugar levels
- Difficulty in sleeping
- Increased blood pressure
- Anaemia (low red blood cell)
- Dizziness
- Localised or general abdominal pain
- Constipation
- Indigestion
- Localised pain
- Reduction in platelets

Uncommon (may affect up to 1 in 100 people):
- Inflammation of the vagina or genital area in women
- Sensations such as tingling or feeling numb
- Swollen, sore, or discoloured tongue
- Dry mouth
- Pain at and around the place where the infusion (drip) was given
- Inflammation of the veins (including where the infusion (drip) was given)
- A need to urinate more often
- Chills
- Feeling thirsty
- Increased sweating
- Hyponatraemia (low blood sodium levels)
- Kidney failure
- Abdominal bloating
- Injection site pain
- Increase in creatinine
- Stomach pain
- Changes in heart rate (e.g. increase rate)
- Decrease of the blood cell count
- Weakness and/or sensory changes

Rare (may affect up to 1 in 1000 people):
- Superficial tooth discolouration, removable with professional dental cleaning (manual descaling)

The following side effects have also been reported (**Not known:** frequency cannot be estimated from the available data):
- Alopecia (hair loss)

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via HPRA Pharmacovigilance, Website: www.hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Linezolid

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the packaging after EXP. The expiry date refers to the last day of that month.

Do not store above 30°C.
Store in the original package in order to protect from light.

After opening: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature in primary bag after removal of the secondary pack (pouch). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Do not use this medicine if you notice that solution is not clear, colourless to yellow or to yellowish-brown.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Linezolid contains
- The active substance is linezolid. 1 ml of solution for infusion contains 2 mg linezolid. Each 300 ml infusion bag contains 600 mg linezolid.
- The other ingredients are glucose monohydrate, sodium citrate dihydrate, citric acid, hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections. See section 2 "Linezolid contains glucose and sodium."

What Linezolid looks like and contents of the pack
Clear, colourless to yellow or to yellowish-brown solution (pH: 4.6 – 5.2, osmolality: 270 mOsmol/kg – 320 mOsmol/kg).

Linezolid solution for infusion:
Primary packaging:
multilayer polyolefin plastic bag (300 ml) with multilayer polyolefin plastic port tube and polyolefin twist off connector.
Secondary packaging:
Overpouch bag made of multilayer film. Film layers of bag from outside to inside: polyester, aluminium, polyester, propylene, 1 and 10 in a box.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
KRKA, d.d., Novo mesto, Šmarješka cesta 6, 8501 Novo mesto, Slovenia

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Austria, Hungary, Czech Republic, Slovak Republic, Estonia, Latvia, Lithuania, Poland, Slovenia, Croatia, Romania, Italy,	Linezolid Krka
Ireland, United Kingdom (Northern Ireland)	Linezolid
Bulgaria	Линезолид Крка
Germany	Linezolid TAD
Portugal	Linezolida Krka

This leaflet was last revised in June 2025.

The following information is intended for healthcare professionals only:

Linezolid 2 mg/ml solution for infusion
linezolid
IMPORTANT: Refer to Summary of Product Characteristics before prescribing.

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

Description
For single use only. The bag holds 300 ml solution and is packaged in a box. Each box contains 1 or 10 infusion bags.
Linezolid 2 mg/ml solution for infusion contains linezolid 2 mg/ml in a clear, colourless to yellow or to yellowish-brown solution. Other ingredients are glucose monohydrate, sodium citrate dihydrate, citric acid, hydrochloric acid, sodium hydroxide and water for injection.

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

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

The recommended linezolid dosage should be administered IV twice daily.

Recommended dosage and duration 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 have not yet been established for treatment periods longer than 28 days.

No increase in the recommended dosage or duration of treatment is required for infections associated with concurrent bacteraemia. The dose recommendation for the solution for infusion and the tablets/granules for oral suspension are identical and are as follows:

Infections	**Dosage and route for twice daily administration**	**Duration of treatment**
Nosocomial pneumonia	600 mg twice daily	10-14 Consecutive Days
Community acquired pneumonia		
Complicated skin and soft tissue infections	600 mg twice daily	

Paediatric population: The safety and efficacy of linezolid in children aged (< 18 years old) has not been established. Currently available data are described in section 4.8, 5.1, and 5.2 of the SmPC but no recommendation on a posology can be made.

Elderly: No dose adjustment is required.

Renal impairment: No dose adjustment is required.

Severe renal impairment (i.e. 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).

Hepatic impairment: Patients with mild to moderate hepatic insufficiency (Child-Pugh class A or B): No dose adjustment is required.

Severe hepatic impairment (Child-Pugh class C): As linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism and, therefore, no dose adjustment is recommended. 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.

Contraindications
Hypersensitivity to linezolid or to any of the excipients.

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 medications:

• Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
• Patients taking any of the following medications: Serotonin re-uptake inhibitors, 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. adrenaline / epinephrine, noradrenaline / norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

Breast feeding should be discontinued prior to and throughout administration.

Special warnings and precautions for use

Myelosuppression

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pretreatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than younger patients. Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis. Therefore, close monitoring of blood counts is recommended in patients who: have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 10-14 days of therapy. Linezolid should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible.

If significant myelosuppression occurs during linezolid therapy, treatment should be stopped unless it is considered absolutely necessary to continue therapy, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented.

In addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count.

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

Cases of sideroblastic anaemia have been reported post-marketing. Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered following discontinuation of linezolid with or without treatment for their anaemia.

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

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 drug. More patients in the linezolid arm acquired Gram negative pathogens during the study and died from infection caused by Gram negative pathogens and polymicrobial infections. Therefore, in complicated skin and soft tissue infections 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. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Antibiotic-associated diarrhoea and colitis
Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, has 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. Drugs inhibiting peristalsis are contraindicated in this situation.

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

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

Serotonin syndrome
Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and opioids have been reported (see section 4.5 of SmPC). Co-administration of linezolid and serotonergic agents is therefore contraindicated (see section 4.3 of SmPC) 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.

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.

Hyponatraemia and SIADH
Hyponatraemia and/or Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) have been observed in some patients treated with linezolid. It is recommended that serum sodium levels are monitored regularly in patients at risk of hyponatraemia such as elderly patients or patients taking medicines that may lower blood sodium levels (e.g. thiazide diuretics such as hydrochlorothiazide).

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

All patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary. 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.
There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis.

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

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

Use with tyramine-rich foods
Patients should be advised against consuming large amounts of tyramine rich foods.

Superinfection
The effects of linezolid therapy on normal flora have not been evaluated in clinical trials.
The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. For example, approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

Special populations
Linezolid should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk (see sections 4.2 and 5.2 of the SmPC).
It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk.

Impairment of fertility
Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans; possible effects of linezolid on the human male reproductive system are not known.

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

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

Excipients
300 ml of the solution contains 13.7 g glucose. This should be taken into account in patients with diabetes mellitus.

300 ml of the solution also contains 114 mg sodium (5 mmol), equivalent to 5.7 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Interactions

Monoamine oxidase inhibitors

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients on concomitant medications 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.

Potential interactions producing elevation of blood pressure

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 mm Hg, compared with 11-15 mm Hg increases with linezolid alone, 14-18 mm Hg with either pseudoephedrine or phenylpropanolamine alone and 8-11 mm Hg with placebo. Similar studies in hypertensive subjects have not been conducted. It is recommended that doses of drugs with a vasopressive action, including dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered with linezolid.

Potential serotonergic interactions

The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20 mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

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

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

Use with tyramine-rich foods

No significant pressor response was observed in subjects receiving both linezolid and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting excessive amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

Drugs metabolised by cytochrome P450

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 drug interactions are expected with linezolid.

Rifampicin

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

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

Fertility, pregnancy and lactation
Pregnancy
There are limited data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity. 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.

Breast-feeding
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.

Effects on ability to drive and use machines
Patients should be warned about the potential for dizziness or symptoms of visual impairment whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs.

Undesirable effects
The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 6,000 adult patients who received the recommended linezolid doses for up to 28 days. Those most commonly reported were diarrhoea (8.9%), nausea (6.9%) and vomiting (4.3%) and headache (4.2%).

The most commonly reported drug-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 drug-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.

The following undesirable effects have been observed and reported during treatment with linezolid with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); Not known (cannot be estimated from the available data)

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Frequency not known (cannot be estimated from available data)**
Infections and infestations	candidiasis, oral candidiasis, vaginal candidiasis, fungal infections	antibiotic-associated colitis, including pseudomembranous colitis*, vaginitis		
Blood and the lymphatic	thrombocytopenia*, anaemia*†	pancytopenia*, leucopenia*,	sideroblastic anaemia*	myelosuppresion*,

system disorders		neutropenia, eosinophilia		
Immune system disorders			anaphylaxis	
Metabolism and nutrition disorders		hyponatraemia	lactic acidosis*	
Psychiatric disorders	insomnia			
Nervous system disorders	headache, taste perversion (metallic taste), dizziness	convulsions*, peripheral neuropathy* hypoaesthesia, paraesthesia		serotonin syndrome**
Eye disorders		optic neuropathy*, blurred vision*	changes in visual field defect*	optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
Ear and labyrinth disorders		tinnitus		
Cardiac disorders		arrhythmia (tachycardia)		
Vascular disorders	hypertension	transient ischaemic attacks, phlebitis, thrombophlebitis		
Gastrointestinal disorders	diarrhoea, nausea, vomiting, localised or general abdominal pain, constipation, dyspepsia	pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder	superficial tooth discolouration	
Hepato-biliary disorders	abnormal liver function test; increased AST, ALT or alkaline phosphatase	increased total bilirubin		
Skin and subcutaneous tissue disorders	pruritus, rash	angioedema, urticaria, dermatitis bullous, dermatitis, diaphoresis	toxic epidermal necrolysis[#], Stevens-Johnson syndrome[#], hypersensitivity vaculitis	alopecia
Musculoskeletal and connective tissue disorders			rhabdomyolysis*	
Renal and urinary disorders	increased BUN	renal failure, increased creatinine,		

		polyuria		
Reproductive system and breast disorders		vulvovaginal disorder		
General disorders and administration site conditions	fever, localised pain	chills, fatigue, injection site pain, increased thirst		
Investigations	Chemistry Increased LDH, creatine kinase, lipase, amylase or non fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate. Haematology Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.	Chemistry Increased sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride. Haematology Increased reticulocyte count. Decreased neutrophils.		

***** See section ‘‘Special Warnings and precautions for use”.
****** See sections ‘‘Contraindications” and ‘‘Interactions”
[#] ADR frequency estimated using "The Rule of 3"
† See below

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

[†]In controlled clinical trials where linezolid was administered for up to 28 days, 2.0% of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for >28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for >28 days.

Paediatric population
Safety data from clinical studies based on more than 500 paediatric patients (from birth to 17 years) do not indicate that the safety profile of linezolid for paediatric patients differs from that for adult patients.

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.

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

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

Incompatibilities
Additives should not be introduced into this solution. If linezolid is to be given concomitantly with other drugs, each drug should be given separately in accordance with its own directions for use. Similarly, if the same intravenous line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following linezolid administration with a compatible infusion solution.

Linezolid Solution for Infusion is known to be physically incompatible with the following compounds: amphotericin B, chlorpromazine hydrochloride, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and sulphamethoxazole / trimethoprim. Additionally, it is chemically incompatible with ceftriaxone sodium.

Shelf life
2 years
After opening: Chemical and physical in-use stability has been demonstrated for 24 hours at room temperature in primary bag after removal of the secondary pack (pouch). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Special precautions for storage
Do not store above 30°C.
Store in the original package in order to protect from light.