

| Package Leaflet: Information for the user |
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| Linezolid Rowex 2 mg/ml Solution for infusion |
| Linezolid |
| Read all of this leaflet carefully before you start using this medicine because it contains important information for you. <ul style="list-style-type: none">Keep this leaflet. You may need to read it again. If you have any further questions, ask your doctor, pharmacist or nurse. This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4. |
| What is in this leaflet: <ol style="list-style-type: none">What Linezolid Rowex is and what it is used for What you need to know before you use Linezolid Rowex How to use Linezolid Rowex Possible side effects How to store Linezolid Rowex Contents of the pack and other information |

1 What Linezolid Rowex is and what it is used for

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

2 What you need to know before you use Linezolid Rowex

Do not use Linezolid Rowex

- If you are allergic (hypersensitive) 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 (MAOs: for example phenelzine, isocarboxazid, selegiline, moclobemide). These medicinal products may be used to treat depression or Parkinson’s disease;
- If you are breast-feeding. This is because Linezolid Rowex passes into breast milk and could affect the baby.

Warnings and precautions

Linezolid Rowex 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?
- Are you taking any of the following medicines?
 - decongestant, cold or flu remedies containing pseudoephedrine or phenylpropanolamine
 - medicines used to treat asthma such as salbutamol, terbutaline, fenoterol
 - antidepressants known as tricyclics or SSRIs (selective serotonin reuptake inhibitors) for example amitriptyline, cipramil, 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
 - used to treat moderate to severe pain, such as pethidine
 - medicines used to treat anxiety disorders, such as buspirone
 - an antibiotic called rifampicin.

Take special care with Linezolid Rowex

Talk to your doctor, pharmacist or nurse before using Linezolid Rowex if you

- 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 Rowex. If this becomes severe or persistent or you notice that your stool contains blood or mucus, you should stop taking Linezolid Rowex 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.

Other medicines and Linezolid Rowex

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

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

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Tell your doctor if you are taking or have taken within the last 2 weeks the following medicines as Linezolid Rowex **must not** be taken if you are already taking these medicines or have taken them recently. (See also Section 2 above ‘Do not use Linezolid Rowex’).

- monoamine oxidase inhibitors (MAOs 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 Rowex, 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, cipramil, 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
- Medicines used to treat moderate to severe pain, such as pethidine
- Medicines used to treat anxiety disorders, such as buspirone
- Medicines that stop blood clotting, such as warfarin.

Linezolid Rowex with food and drink

- You can use Linezolid Rowex 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 this medicine 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 or pharmacist immediately.

Pregnancy, breast-feeding and fertility

The effect of Linezolid Rowex in pregnant women is not known. Therefore it should not be used in pregnancy unless advised by your doctor. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

You should not breast-feed when using Linezolid Rowex because it passes into breast milk and could affect the baby.

Driving and using machines

Linezolid Rowex 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 Rowex contains glucose and sodium

Glucose

Each 1 ml of Linezolid Rowex solution contains 48 mg glucose (14.4 g glucose in one bag). Please tell your doctor or nurse if you are diabetic.

Sodium

Each 1 ml of Linezolid Rowex solution contains 0.38 mg sodium (114 mg sodium in one bag). Please tell your doctor, pharmacist or nurse if you are on a low sodium diet.

3 How to use Linezolid Rowex

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults

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 Rowex) 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 Rowex after dialysis.

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 using Linezolid Rowex, your doctor should perform regular blood tests to monitor your blood count.

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

Use in children and adolescents

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

If you receive more Linezolid Rowex than you should?

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

If you miss a dose of Linezolid Rowex

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.

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 Rowex :

- skin reactions such as red sore skin and flaking (dermatitis), rash, itching, or swelling, particularly around the face and neck. This may be the sign of an allergic reaction and it may be necessary for you to stop taking Linezolid Rowex.
- problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted
- 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
- recurrent nausea or vomiting, abdominal pain or rapid breathing
- fits or seizures have been reported with Linezolid Rowex . You should let your doctor know if you experience agitation, confusion, delirium, rigidity, tremor, incoordination and seizure while also taking antidepressants known as SSRIs (see section 2).

Numbness, tingling or blurred vision have been reported by patients who have been given Linezolid Rowex 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 your kidney or liver function or blood sugar levels
 - 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
 - Difficulty in sleeping
 - Increased blood pressure
 - Anaemia (low red blood cell)
 - Changes in numbers of certain cells in the blood which may affect your ability to fight infection
 - Skin rash
 - Itching skin
 - Dizziness
 - Localised or general abdominal pain
 - Constipation
 - Indigestion
 - Localised pain
 - Fever.
- 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
 - Blurred vision
 - “Ringing” in the ears (tinnitus)
 - Inflammation of the veins
 - Dry or sore mouth , swollen, sore, or discoloured tongue
 - 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 tired or thirsty
 - Inflammation of the pancreas
 - Increased sweating
 - Changes in proteins, salts or enzymes in the blood which measure kidney or liver function
 - Convulsions
 - Hyponatraemia (low blood sodium levels)
 - Kidney failure
 - Reduction in platelets.
 - Abdominal bloating
 - 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)
 - Injection site pain
 - Inflammation of the skin
 - Increase in creatinine
 - Stomach pain
 - Changes in heart rate (e.g. increase rate).

This medicinal product is authorised in the Member States of the EEA under the following names:

| | |
|-----------------|--|
| The Netherlands | Linezolid Sandoz 600 mg/300 ml, oplossing voor infusie |
| Austria | Linezolid Sandoz 2mg/ml –Infusionslösung |
| Bulgaria | ЛИНЕЗОЛИД САНДОЗ 2MG/ML ИНФУЗИОНЕН РАСТВОР |
| Czech Republic | LINEZOLID SANDOZ 2 MG/ML INFUZNÍ ROZTOK |
| Germany | Linezolid HEXAL 2 mg/ml Infusionslösung |
| Spain | Linezolid Sandoz 2mg/ml solución para perfusión EFG |
| France | LINEZOLIDE SANDOZ 2 mg/ml, solution pour perfusion |
| Croatia | Linezolid Sandoz 2 mg/ml otopina za infuziju |
| Ireland | Linezolid Rowex 2mg/ml Solution for infusion |
| Italy | Linezolid Sandoz GmbH |
| Poland | Linezolid Sandoz |
| Romania | LINEZOLID SANDOZ 2mg/ml solutie perfuzabila |
| Slovenia | Linezolid Sandoz 2 mg/ml raztopina za infundiranje |
| Slovakia | Linezolid Sandoz 600 mg/300 ml infúzny roztok |
| United Kingdom | Linezolid 2 mg/ml Solution for Infusion |

This leaflet was last revised in 01/2018.

- Restricted field of vision
- Superficial tooth discolouration, removable with professional dental cleaning (manual descaling).

Not known (frequency cannot be estimated from the available data)

- Serotonin syndrome (symptoms include fast heart rate, confusion, abnormal sweating, hallucinations, involuntary movements chills and shivering)
- Lactic acidosis (symptoms include recurrent nausea and vomiting, abdominal pain, rapid breathing)
- Severe skin disorders
- Sideroblastic anaemia (a type of anaemia (low red blood cells))
- Alopecia (hair loss)
- Changes in colour vision or difficulty in seeing detail
- Decrease of the blood cell count
- Weakness and/or sensory changes.

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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: mdsafety@hpra.ie. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Linezolid Rowex

As you will be given this medicine under close medical supervision, hospital staff will comply with the following advices:

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 bag after EXP. The first two digits indicate the month and the last four digits indicate the year. The expiry date refers to the last day of that month. Use the medicine as soon as the seal is broken.

Do not use this medicine if you notice that the solution is not clear and contains particles.

Keep this medicine correctly in its box and foil wrapping in order to protect from light.

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

6 Contents of the pack and other information

What Linezolid Rowex contains

- The active substance is linezolid. Each 1ml of solution contains 2 mg linezolid. Each 300 ml infusion bag contains 600 mg linezolid
- The other ingredients are glucose monohydrate (a type of sugar), sodium citrate (E331), citric acid anhydrous (E330), hydrochloric acid (E507; as 10% solution) for pH-adjustment or sodium hydroxide (E524; as 10% solution) for pH-adjustment and water for injections.

What Linezolid Rowex looks like and contents of the pack

Linezolid Rowex is presented as a clear solution in single infusion bags

Each box contains 1, 2, 5, 10, 20 or 25 infusion bag(s). Additionally, hospital packaging of 3, 5, 6, 10 or 20 boxes containing either 1 or 2 infusion bag(s) are available.

Not all package sizes may be marketed.

Marketing Authorisation Holder and Manufacturers

Marketing Authorisation Holder

Rowex Ltd., Bantry, Co. Cork, Ireland.

Manufacturer(s)

Synthon BV, Microweg 22, 6545 CM Nijmegen, The Netherlands.
Synthon Hispania SL, C/ Castelló no1, Pol. Las Salinas, Sant Boi de Llobregat, 08830 Barcelona, Spain.
Sandoz GmbH, Biochemiestrasse, 6250 Kundl, Austria.
Salutas Pharma GmbH, Otto-von-Guericke-Allee 1, Sachsen-Anhalt, 39179 Barleben, Germany.
Lek Pharmaceuticals d.d., Verovškova ulica 57, 1526 Ljubljana, Slovenia.

This medicinal product is authorised in the Member States of the EEA under the following names:

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| Czech Republic | LINEZOLID SANDOZ 2 MG/ML INFUZNÍ ROZTOK |
| Germany | Linezolid HEXAL 2 mg/ml Infusionslösung |
| Spain | Linezolid Sandoz 2mg/ml solución para perfusión EFG |
| France | LINEZOLIDE SANDOZ 2 mg/ml, solution pour perfusion |
| Croatia | Linezolid Sandoz 2 mg/ml otopina za infuziju |
| Ireland | Linezolid Rowex 2mg/ml Solution for infusion |
| Italy | Linezolid Sandoz GmbH |
| Poland | Linezolid Sandoz |
| Romania | LINEZOLID SANDOZ 2mg/ml solutie perfuzabila |
| Slovenia | Linezolid Sandoz 2 mg/ml raztopina za infundiranje |
| Slovakia | Linezolid Sandoz 600 mg/300 ml infúzny roztok |
| United Kingdom | Linezolid 2 mg/ml Solution for Infusion |

This leaflet was last revised in 01/2018.

A Guide for Hospital Staff

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

Description

A clear colourless or yellowish polypropylene infusion bag with one port or two ports in a transparent foil laminate overwrap bag. The bag holds 300 ml solution and is packaged in a box. Each box contains 1, 2, 5, 10, 20 or 25 infusion bag(s). Additionally, hospital packaging of 3, 5, 6, 10 or 20 boxes containing either 1 or 2 infusion bag(s) are available.

Linezolid Rowex 2 mg/ml solution for infusion contains linezolid 2 mg/ml in an isotonic, clear, colourless to yellow solution. Other ingredients are: glucose monohydrate, sodium citrate (E331), citric acid anhydrous (E330), hydrochloric acid (E507; as 10% solution) for pH-adjustment or sodium hydroxide (E524, as 10% solution) for pH-adjustment, water for injections.

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 or orally twice daily.

Recommended dosage and duration of treatment for adults:

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

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

The maximum treatment duration is 28 days.

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

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

Elderly patients: No dose adjustment is required.

Patients with renal insufficiency: No dose adjustment is required.

Patients with severe renal insufficiency (i.e. CL_{cr} < 30 ml/min): No dose adjustment is required. Due to the unknown clinical significance of higher exposure (up to 10-fold) to the two primary metabolites of linezolid in patients with severe renal insufficiency, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

As approximately 30 % of a linezolid dose is removed during 3 hours of haemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by haemodialysis, but the concentrations of these metabolites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency. Therefore, linezolid should be used with special caution in patients with severe renal insufficiency who are undergoing dialysis, and only when the anticipated benefit is considered to outweigh the theoretical risk.

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

Patients with hepatic insufficiency: No dose adjustment is required. However, there are limited clinical data and it is recommended that linezolid should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.

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. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding 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 2

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 anti-depressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of linezolid and serotonergic agents is therefore contraindicated 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.

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 antidepressive 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.

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

Each ml of the solution contains 48 mg (i.e. 14.4 g/300 ml) glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance. Each ml of solution also contains 0.38 mg (114 mg/300 ml) sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

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), cases of serotonin syndrome have been reported. Therefore, while co-administration is contraindicated, 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.

Pregnancy and Lactation

Pregnancy

There are no adequate 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 2,000 adult patients who received the recommended linezolid doses for up to 28 days.

Those most commonly reported were diarrhoea (8.4%), headache (6.5%), nausea (6.3%) and vomiting (4.0%).

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) | Very Rare (<1/10,000) | Frequency not known (cannot be estimated from available data) |
|---|--|--|--|-----------------------|--|
| Infections and infestations | Candidiasis, oral candidiasis, vaginal candidiasis, fungal infections | Vaginitis | Antibiotic-associated colitis, including pseudomembranous colitis* | | |
| Blood and the lymphatic system disorders | Anaemia*†, | Leucopenia*, neutropenia, thrombocytopenia*, eosinophilia | Pancytopenia* | | Myelosuppression*, sideroblastic anaemia* |
| Immune system disorders | | | | | Anaphylaxis |
| Metabolism and nutrition disorders | | Hyponatraemia | | | Lactic acidosis* |
| Psychiatric disorders | Insomnia | | | | |
| Nervous system disorders | Headache, taste perversion (metallic taste), Dizziness | Convulsions*, hypoaesthesia, paraesthesia | | | Serotonin syndrome**, peripheral Neuropathy* |
| Eye disorders | | Blurred vision* | Changes in visual field defect* | | Optic neuropathy*, 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 discoloration or disorder | Superficial tooth discolouration | | |
| Hepatobiliary disorders | Abnormal liver function test, increased AST, ALT or alkaline phosphatase | Increased total bilirubin | | | |
| Skin and subcutaneous tissue disorders | Pruritus, rash | Urticaria, dermatitis, diaphoresis | | | Bullous disorders such as those described as Stevens-Johnson syndrome and toxic epidermal necrolysis, angioedema, alopecia |
| 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. <p>Haematology Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.</p> | Chemistry Increased sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride. <p>Haematology Increased reticulocyte count. Decreased neutrophils.</p> | | | |

* See section Special Warnings and Precautions for Use

** See sections Contraindications and Interactions

† 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. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

Signs of toxicity in rats following doses of 3000 mg/kg/day linezolid were decreased activity and ataxia whilst dogs treated with 2000 mg/kg/day experienced vomiting and tremors.

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. Do not reconnect partially used bags.

Linezolid Rowex 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 Rowex 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.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf Life

Before opening: 30 months

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

Special Precautions for Storage

Store in the original package (overwrap and carton) in order to protect from light.

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|--------------------------|---|---------------------------------|-----------------------------|------------------------|--|--|--|--|--|--|----------------------|
| Artwork Checklist | Job Description Linezolid PIL Renewal 01-18 | Version Number 01 | Size 440 x 480 mm | Ink ■ | | | | | | | ACCF 20334 |
| | Market IM | Proof Date 15/01/2018 | Colour Ref. N/A | Colour Black | | | | | | | |
| | | | | Print ✓ | | | | | | | |
| | | | | Sign ✓ | | | | | | | |