

## Package leaflet: Information for the user

### Linezolid Polpharma 2 mg/ml oplossing voor infusie

#### Linezolid

**Read all of this leaflet carefully before you are given this medicine 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 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 or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### What is in this leaflet

1. What Linezolid Polpharma is and what it is used for
2. What you need to know before you are given Linezolid Polpharma
3. How Linezolid Polpharma is given
4. Possible side effects
5. How to store Linezolid Polpharma
6. Contents of the pack and other information

#### 1. What Linezolid Polpharma is and what it is used for

Linezolid Polpharma 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 in adults. Your doctor will have decided if this medicine is suitable to treat your infection.

#### 2. What you need to know before you are given Linezolid Polpharma

##### **You must not be given Linezolid Polpharma:**

- 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 breastfeeding. This is because linezolid passes into breast milk and could affect the baby.

Linezolid Polpharma 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, schizo affective disorder, mental confusion or other mental problems?
- Do you take any opioids?

- 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, ciproamil, 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
  - an antibiotic called rifampicin

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

### Warnings and precautions

Tell your doctor before you are treated with this medicine if you:

- bruise and bleed easily
- are anaemic
- are prone to getting infections
- have a history of seizures
- have liver problems or kidney problems particularly if you have 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 Polpharma. If this becomes severe or persistent or you notice that your stool contains blood or mucus, you should stop Linezolid Polpharma treatment 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 over breathing

### Other medicines and Linezolid Polpharma

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

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

- 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 Polpharma, 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, desvenlafaxine, 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.

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

### **Linezolid Polpharma with food, drink and alcohol**

- 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, to cause an increase in your blood pressure.
- If you develop a throbbing headache after eating or drinking, tell your doctor or pharmacist immediately.

### **Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before you are given this medicine.

The effect of Linezolid Polpharma in pregnant women is not known. Therefore you should not be given this medicine if you are pregnant, unless your doctor advises it.

You must not breastfeed when being given Linezolid Polpharma because it passes into breast milk and could affect the baby.

### **Driving and using machines**

Linezolid Polpharma 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**

Each ml of Linezolid Polpharma contains 45.7 mg of glucose (13.7 g glucose in one bag). This should be taken into account in patients with diabetes mellitus.

#### **Sodium**

Each ml of Linezolid Polpharma contains 0.61 mg of sodium (0.182 g sodium in one bag). To be taken into consideration by patients on a controlled sodium diet.

### **3. How Linezolid Polpharma is given**

You can take Linezolid Polpharma either before, during or after a meal.

#### **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) 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 this medicine 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 being given Linezolid Polpharma, your doctor should perform regular blood tests to monitor your blood count.

Your doctor should monitor your eyesight if you are given this medicine for more than 28 days.

#### **Use in children and adolescents**

Linezolid Polpharma is not recommended in children and adolescents (under 18 years old).

#### **If you receive more Linezolid Polpharma than you should**

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

#### **If you miss a dose of Linezolid Polpharma**

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.

If you have any further questions on the use of this medicine, ask your doctor 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 Polpharma:

- 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 treatment with Linezolid Polpharma.
- 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 this medicine.

- serotonin syndrome (frequency 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).

Numbness, tingling or blurred vision have been reported by patients who have been given this medicine 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 side effects: (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 side effects: (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)

**Rare side effects: (may affect up to 1 in 1000 people):**

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

**The following side effects have also been reported (frequency not known):**

- 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 nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via  
Nederlands Bijwerken Centrum Lareb  
Website: [www.lareb.nl](http://www.lareb.nl)

By reporting side effects you can help provide more information on the safety of this medicine.

**5. How to store Linezolid Polpharma is stored**

Hospital staff will make sure that Linezolid Polpharma is not used after the “Use by” date printed on the bag and that it is given to you as soon as the seal is broken. They will also visually inspect the solution prior to use and only clear solution, without particles will be used. They will also make sure that the solution is kept correctly in its carton box and in order to protect from light and out of the reach and sight of children until it is needed.

**6. Contents of the pack and other information**

**What Linezolid Polpharma contains**

- The active substance is linezolid. Each ml of solution contains 2 mg of linezolid.
- The other ingredients are: glucose monohydrate (a type of sugar), sodium citrate (E331), citric acid anhydrous (E330), hydrochloric acid (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

**What Linezolid Polpharma looks like and contents of the pack**

Linezolid Polpharma is a clear colourless to yellow solution.

This medicine is packaged in a single use, low density polyethylene bags (LDPE) molded with adapter type Insocap containing 300 ml of solution (600 mg of linezolid). Each box contains 1 or 10 polyethylene bags.

Not all pack sizes may be marketed

**Marketing Authorisation Holder**

Zakłady Farmaceutyczne POLPHARMA S.A.  
ul. Pelplińska 19, 83-200 Starogard Gdański

**Manufacturer**

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Warszawskie Zakłady Farmaceutyczne Polfa S.A.  
ul. Karolkowa 22/24  
01-207 Warszawa

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

Nederland: Linezolid Polpharma  
Bulgarije: Linezolid Polpharma  
Tsjechische Republiek: LINEZA 2 mg/ml infuzní roztok  
Letland: Linezolid Medana 2 mg/ml šķīdums infūzijām  
Litouwen: Linezolid Medana 2 mg/ml infuzinis tirpalas  
Polen: Linezolid Polpharma  
Slowakije: LINEZA 2 mg/ml infúzny roztok

**This leaflet was last revised in February 2024.**

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The following information is intended for healthcare professionals only:

**IMPORTANT:** Refer to Summary of Product Characteristics before prescribing.

Linezolid Polpharma 2 mg/ml oplossing voor infusie 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 (for pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

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.

**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 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:

<b>Infections</b>	<b>Dosage</b>	<b>Duration of treatment</b>
Nosocomial pneumonia	600 mg twice daily	10-14 Consecutive days
Community acquired pneumonia	600 mg twice daily	10-14 Consecutive days
Complicated skin and soft tissue infections	600 mg twice daily	10-14 Consecutive days

*Paediatric population:* There are insufficient data on the pharmacokinetics, 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<sub>cr</sub> < 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:* Patients with mild to moderate hepatic insufficiency (Child-Pugh class A or B): No dose adjustment is required:

Patients with severe hepatic insufficiency (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 no pharmacokinetic data and limited clinical experience of linezolid in patients with severe hepatic



insufficiency. Linezolid should be used with special caution in patients with severe hepatic insufficiency and 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, pheochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
- Patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT<sub>1</sub> 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.

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 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*

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

Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and *Clostridium difficile*-associated diarrhoea, 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. 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 Polpharma 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 Polpharma 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.

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk.

#### *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*

This medicine contains 45.67 mg/ml (i.e. 13.702 g/300 ml) of glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance. This medicine contains 0.61 mg/ml (i.e. 0.182 g/300 ml) of 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 mmHg, compared with 11-15 mmHg increases with linezolid alone, 14 - 18 mmHg with either pseudoephedrine or phenylpropanolamine alone and 8 - 11 mmHg with placebo. Similar studies in hypertensive subjects have not been conducted. It is recommended that doses of 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 management of patients for whom treatment with linezolid and serotonergic agents is essential, is describe 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  $C_{max}$  and AUC by a mean 21% [90% CI, 15, 27] and a mean 32% [90% CI, 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown.

#### *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 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.

#### Breastfeeding

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.

It is not known whether these findings have an impact on human 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.

### **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. Check for minute leaks by squeezing the polyethylene 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.

Polyethylene bag after checking the tightness and removing protective film, should be connected to the set with dual channel needle.

Do not use these polyethylene bags in series connections. Any unused solution must be discarded. Do not reconnect partially used bags.

**Compatibilities**

Linezolid Polpharma solution is compatible with the following solutions: 5% glucose intravenous infusion, 0.9 % sodium chloride intravenous infusion, Ringer-lactate 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 Polpharma 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**

Before opening: 30 months

After opening: The chemical and physical in-use stability has been demonstrated for 2 hours at 25°C. 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**

This medicinal product does not require any special temperature storage conditions, keep the polyethylene bag in the outer carton box in order to protect from light.

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