Public Assessment Report

Decentralised Procedure

Linezolid 2 mg/ml Solution for Infusion
PL 36780/0001

UK/H/5511/001/DC

Infomed Fluids Srl
Lay Summary

Linezolid 2 mg/ml Solution for Infusion
(linezolid)

This is a summary of the public assessment report (PAR) for Linezolid 2 mg/ml Solution for
Infusion (PL 36780/0001; UK/H/5511/001/DC). Linezolid 2 mg/ml Solution for Infusion will
be referred to as Linezolid 2 mg/ml Infusion in this report, for ease of reading. It explains
how Linezolid 2 mg/ml Infusion was assessed and its authorisation recommended as well as
its conditions of use. It is not intended to provide practical advice on how to use Linezolid
2 mg/ml Infusion.

For practical information about using Linezolid 2 mg/ml Infusion, patients should read the
package leaflet or contact their doctor or pharmacist.

What is Linezolid 2 mg/ml Infusion and what is it used for?
Linezolid 2 mg/ml Infusion is a ‘generic medicine’. This means that it is similar to a
‘reference medicine’, already authorised in the European Union (EU) called Zyvox 2mg/ml
Solution for Infusion.

Linezolid 2 mg/ml Infusion is used to treat pneumonia and some infections in the skin or
under the skin.

How do Linezolid 2 mg/ml Infusion work?
Linezolid 2 mg/ml Infusion is an antibiotic of the oxazolidinones group. The active substance
in this medicine, linezolid, works by stopping the growth of certain bacteria (germs) that
cause infections.

How is Linezolid 2 mg/ml Infusion used?
Linezolid 2 mg/ml Infusion will be given to the patient through a drip (by infusion into the
vein) by a doctor or healthcare professional.

Please read Section 3 of the package leaflet for detailed information on dosing
recommendations, the route of administration, and the duration of treatment.

The recommended dose for adults (18 years and older) is 300 ml (600 mg linezolid) twice
daily, which is given over a period of 30 to 120 minutes. A course of treatment usually lasts
10 to 14 days but can last up to 28 days. For patients on kidney dialysis Linezolid 2 mg/ml
Infusion should be given after dialysis.

Linezolid 2 mg/ml Infusion can only be obtained with a prescription.

How has Linezolid 2 mg/ml Infusion been studied?
No additional studies were needed as Linezolid 2 mg/ml Infusion is a generic medicine that is
given by infusion and contains the same active substance as the reference medicine, Zyvox
2 mg/ml Solution for Infusion.

What are the possible side effects of Linezolid 2 mg/ml Infusion?
Because Linezolid 2 mg/ml Infusion is a generic medicine, its benefits and possible side
effects are taken as being the same as those of the reference medicine.
For further information, please see the package leaflet.

**Why is Linezolid 2 mg/ml Infusion approved?**
It was concluded that, in accordance with EU requirements, Linezolid 2 mg/ml Infusion has been shown to have comparable quality and be comparable to Zyvox 2 mg/ml Solution for Infusion. Therefore, the view was that, as for Zyvox 2 mg/ml Solution for Infusion, the benefits outweigh the identified risks.

**What measures are being taken to ensure the safe and effective use of Linezolid 2 mg/ml Infusion?**
A Risk Management Plan has been developed to ensure that Linezolid 2 mg/ml Infusion is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the package leaflet for Linezolid 2 mg/ml Infusion, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

**Other information about Linezolid 2 mg/ml Infusion**
Austria, France, Germany, Italy, Poland, Romania, Spain and the UK agreed to grant marketing authorisations for Linezolid 2 mg/ml Infusion on 09 March 2015. The marketing authorisations in the UK were granted on 02 April 2015.

The full PAR for Linezolid 2 mg/ml Infusion follows this summary.

For more information about treatment with Linezolid 2 mg/ml Infusion, read the package leaflet or contact your doctor or pharmacist.

This summary was last updated in May 2015.
TABLE OF CONTENTS

I  Introduction  Page 5
II  Quality aspects  Page 7
III Non-clinical aspects  Page 9
IV  Clinical aspects  Page 9
V  User consultation  Page 15
VI  Overall conclusion, benefit/risk assessment and recommendation  Page 16

Table of content of the PAR update for MRP and DCP  Page 21
I Introduction

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Linezolid 2 mg/ml Infusion (PL 36780/0001; UK/H/5511/001/DC) could be approved. This application was submitted via the Decentralised Procedure, with the UK as Reference Member State (RMS) and Austria, France, Germany, Italy, Poland, Romania and Spain as Concerned Member States (CMS).

Linezolid 2 mg/ml Infusion is a prescription-only medicine (POM), which is indicated for:

- nosocomial pneumonia
- community acquired pneumonia

Linezolid is indicated in adults for the treatment of community acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram-positive bacteria. In determining whether Linezolid 2 mg/ml Infusion is an appropriate treatment, the results of microbiological tests or information on the prevalence of resistance to antibacterial agents among Gram-positive bacteria should be taken into consideration. (See section 5.1 for the appropriate organisms).

Linezolid is not active against infections caused by Gram-negative pathogens.

Specific therapy against Gram-negative organisms must be initiated concomitantly if a Gram-negative pathogen is documented or suspected.

- complicated skin and soft tissue infections

Linezolid is indicated in adults for the treatment of complicated skin and soft tissue infections only when microbiological testing has established that the infection is known to be caused by susceptible Gram-positive bacteria.

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 (see section 4.4). In these circumstances treatment against Gram-negative organisms must be initiated concomitantly.

Treatment with 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.

**Consideration should be given to official guidance on the appropriate use of antibacterial agents.**

This application was made under Article 10(1) of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product. The reference medicinal product, which has been authorised in accordance with Community provisions in force for not less than 10 years in the European Economic Area (EEA), is Zyvox 2 mg/ml Solution for Infusion; this product was authorised to Pharmacia Limited on 05 January 2001 (PL 00032/0259). The licence for Zyvox 2 mg/ml Solution for Infusion subsequently underwent a change of ownership procedure to the current MA holder, Pfizer Limited, on 07 November 2014 (PL 00057/1066).
This medicinal product contains the active substance linezolid. Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. It has in vitro activity against aerobic Gram positive bacteria and some anaerobic micro-organisms. Linezolid selectively inhibits bacterial protein synthesis by binding to a site on the bacterial ribosome (23S of the 50S subunit) and preventing the formation of a functional 70S initiation complex, which is an essential component of the translation process.

No new non-clinical or clinical data were submitted, which is acceptable given that this application is for a generic medicinal product of an originator product that has been in clinical use for over 10 years. Linezolid 2mg/ml Infusion is indicated for parenteral use only. No bioequivalence studies are required for this type of product according to the Guidance on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **), and the applicant has submitted none. Comparative physico-chemical characteristics have been provided for the proposed product versus the originator product, and pharmaceutical equivalence has been shown.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

A summary of the pharmacovigilance system and Risk Management Plan (RMP) have been provided with this application and are satisfactory.

Since Linezolid 2 mg/ml Infusion is intended for generic substitution, this will not lead to an increased exposure to the environment. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

The RMS and CMS considered that this application could be approved at the end of procedure (Day 210) on 09 March 2015. After a subsequent national phase, licences were granted in the UK on 02 April 2015.
II  Quality aspects

II.1  Introduction
The application for Linezolid 2 mg/ml Infusion is submitted according to Article 10(1) of Directive 2001/83/EC, as amended. The applicant has specified Zyvox 2 mg/ml Solution for Infusion (PL 00057/1066) as the reference medicinal product (MA Holder: Pfizer Limited).

The product is formulated as an isotonic, clear, colourless to yellowish solution, free from visible particles. The pH value of the solution for infusion ranges from 4.6 to 5.0 and the solution has an osmolality between 270 to 330 mOsm/kg. The excipients present are glucose monohydrate, sodium citrate, citric acid anhydrous, hydrochloric acid for pH adjustment, sodium hydroxide for pH adjustment, and water for injections.

Linezolid 2 mg/ml Infusion is packed into a non-latex, multi-layer polyolefine infusion bag fitted with a twist off connector spike port. The bag is wrapped into a protective foil pouch. Each infusion bag contains 300 ml of Linezolid 2 mg/ml Infusion and may be marketed in quantities of one, ten and 25 bags.

II.2  Drug Substance
Linezolid
INN:   Linezolid
Chemical Name:  (S)-N-[(3-[3-Fluoro-4-(morpholinyl)phenyl]-oxo-5-oxazolidyl]methyl] acetamide

Structure:

Molecular formula:  C_{16}H_{20}FN_{3}O_{4}
Molecular weight:  337.35
Appearance:   White to off-white crystalline powder.

An Active Substance Master File (ASMF) has been provided by the active substance manufacturer, covering the manufacture and control of the active substance linezolid.

Synthesis of the drug substance from the designated starting materials has been adequately described, and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant
Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided and comply with the proposed specification.

Suitable specifications have been provided for all packaging used to contain the active substance. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product
Pharmaceutical development
The aim was to develop a generic product with the same qualitative and quantitative composition as the UK reference product, Zyvox 2 mg/ml Solution for Infusion (PL 00057/1066) and to provide the formulation as a ‘ready-to-use’ single dose preparation for intravenous infusion, which is packaged in an existing, conventional, plastic infusion bag.

All the excipients used in the manufacture of the proposed formulation comply with their respective European Pharmacopoeial monographs.

Satisfactory certificates of analysis have been provided for all excipients showing compliance with their proposed specifications.

Comparative physico-chemical characteristics have been provided for the proposed product versus the UK reference product, and pharmaceutical equivalence has been shown.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of these excipients.

Manufacture of the products
A satisfactory batch formula has been provided for the manufacture of the finished product, together with an appropriate account of the manufacturing process. A satisfactory manufacturing process has been validated with pilot scale batches. Full process validation will be conducted on the first three production-scale batches.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described that have been adequately validated, as appropriate. Batch data from the process validation have been provided that comply with the release specifications. Certificates of analysis have been provided for all working standards used.

Stability of the products
Stability studies were performed in accordance with current guidelines on batches of the finished product, packed in the packaging proposed for marketing. The data from these studies support a shelf-life for the finished product of 24 months (unopened) with special
storage conditions of “Store in the original package until ready to use, in order to protect from light” and “Do not freeze”. The product should be used immediately after opening.

Suitable post approval stability commitments have been provided to continue the ongoing stability testing and to conduct stability studies on the first three industrial-scale batches of the finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended for this application.

III Non-clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of Linezolid 2 mg/ml Infusion are well-known. As linezolid is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

The applicant’s non-clinical overview has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

Suitable justification has been provided for non-submission of an Environmental Risk Assessment (ERA). As the application is for a generic version of an already authorised product, it is not expected that environmental exposure will increase following approval of a marketing authorisation for the proposed product.

The grant of a marketing authorisation is recommended for this application.

IV Clinical aspects
IV.1 Introduction
No new clinical data have been submitted for this application. The applicant’s clinical overview on the clinical pharmacology, efficacy and safety of the product has been written by an appropriately qualified person and is adequate.

IV.2 Pharmacokinetics
Bioequivalence studies were not provided and are not necessary to support this application for a parenteral product, in accordance with CPMP guidelines (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**, Guideline on the investigation of bioequivalence). Comparative physico-chemical characteristics have been provided for the proposed product versus the UK reference product, and pharmaceutical equivalence has been shown.

IV.3 Pharmacodynamics
No new data have been submitted and none are required for this generic application.

IV.4 Clinical efficacy
No new studies have been performed and none are required for this generic application.

IV.5 Clinical safety
No new safety data were submitted with this application and none were required.

**IV.6 Risk Management Plan (RMP)**

The marketing authorisation holder has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Linezolid 2 mg/ml Infusion.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

**Summary of safety concerns**

<table>
<thead>
<tr>
<th>Important Identified Risks</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myelosuppression, anaemia, sideroblastic anaemia</td>
<td>Statements in the SPC / PIL as follows:</td>
<td>None</td>
</tr>
<tr>
<td>• Antibiotic associated diarrhoea and colitis</td>
<td>• Warnings in Section 4.4, Undesirable effects in Section 4.8 of the SPC</td>
<td></td>
</tr>
<tr>
<td>• Lactic acidosis</td>
<td>• Warnings in Section 2, Possible side effects in Section 4 of the PIL</td>
<td></td>
</tr>
<tr>
<td>• Mitochondrial dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Serotonin syndrome: risk of use with monoamine oxidase inhibitors or following consumption of tyramine-rich foods.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Peripheral and optic neuropathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Convulsions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Increased risk of fatal outcome in patients with catheter related infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Long term use (use of linezolid for more than 28 days)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Important Potential Risks**

None

**Important Missing Information**

• Exposure during pregnancy and lactation
• Use in renal impairment
• Use in hepatic impairment

**Summary table of risk minimisation measures**

In the PIL the following wording is used:

**2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN LINEZOLID INFUSION**

**Warnings and precautions**

Talk to your doctor, pharmacist or nurse before you are treated with Linezolid Infusion if you

• bruise and bleed easily
• are anaemic (have low red blood cells)
• are prone to getting infections
### 4. POSSIBLE SIDE EFFECTS

**Other side effects include:**

**Common side effects (may affect up to 1 in 10 people):**
- unexplained bleeding or bruising, which may be due to changes in specific cells in the blood which may affect blood clotting or lead to anaemia

**Uncommon side effects (may affect up to 1 in 100 people):**
- reduction in the numbers of cells in the blood which fight against infection

**Not known (frequency cannot be estimated from the available data):**
- Sideroblastic anaemia (a type of anaemia (low red blood cells))

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>4. POSSIBLE SIDE EFFECTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Other side effects include:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Common side effects (may affect up to 1 in 10 people):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• unexplained bleeding or bruising, which may be due to changes in specific cells in the blood which may affect blood clotting or lead to anaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon side effects (may affect up to 1 in 100 people):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• reduction in the numbers of cells in the blood which fight against infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Not known (frequency cannot be estimated from the available data):</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sideroblastic anaemia (a type of anaemia (low red blood cells))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**• Antibiotic-associated diarrhoea, colitis, including Pseudomembranous colitis**

Statements in the SPC / PIL as follows:
- Precautions in Section 4.4 of the SPC, Undesirable effects in Section 4.8 of the SPC
- Precaution in Section 2 of the PIL, Possible side effects in Section 4 of the PIL.

In the PIL the following wording is used:

**2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN LINEZOLID INFUSION**

**Precaution**
- you may develop diarrhoea while taking or after taking antibiotics, including Linezolid Infusion. If this becomes severe or persistent or you notice that your stool contains blood or mucus, you should stop taking Linezolid Infusion immediately and consult your doctor. In this situation, you should not take medicines that stop or slow bowel movement.

**4. POSSIBLE SIDE EFFECTS**

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

**• Lactic acidosis**

Statements in the SPC / PIL as follows:
- Warning in Section 4.4 of the SPC, Undesirable effects in Section 4.8 of the SPC
- Possible side effects in Section 4 of the PIL.
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td>In the PIL the following wording is used:</td>
<td></td>
</tr>
<tr>
<td><strong>4. POSSIBLE SIDE EFFECTS</strong></td>
<td>Other side effects include:</td>
<td></td>
</tr>
<tr>
<td><strong>Not known (frequency cannot be estimated from the available data):</strong></td>
<td>• lactic acidosis (symptoms include recurrent nausea and vomiting, abdominal pain, rapid breathing)</td>
<td></td>
</tr>
<tr>
<td><strong>• Mitochondrial dysfunction</strong></td>
<td>Statements in the SPC / PIL as follows:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Warning in Section 4.4 of the SPC.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within the PIL, the symptoms of mitochondrial dysfunction are listed:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Talk to your doctor or pharmacist immediately if during treatment you suffer from</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• loss of sensitivity in your arms or legs or a sensation of tingling or prickling in your arm or legs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• recurrent nausea or vomiting, abdominal pain or over breathing.</td>
<td></td>
</tr>
<tr>
<td><strong>• Peripheral and optic neuropathy</strong></td>
<td>Statements in the SPC / PIL as follows:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Precaution in Section 4.4 of the SPC, Undesirable effects in Section 4.8 of the SPC, Preclinical safety data in Section 5.3 of the SPC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• What you need to know before you are given Linezolid Infusion in Section 2 of the PIL, Possible side effects in Section 4 of the PIL.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In the PIL the following wording is used:</td>
<td></td>
</tr>
<tr>
<td><strong>2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN LINEZOLID INFUSION</strong></td>
<td>Talk to your doctor or pharmacist immediately if during treatment you suffer from:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.</td>
<td></td>
</tr>
<tr>
<td><strong>4. POSSIBLE SIDE EFFECTS</strong></td>
<td>Tell your doctor, or pharmacist or nurse immediately if you notice any of these side effects during your treatment with Linezolid Infusion:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.</td>
<td></td>
</tr>
</tbody>
</table>
Linezolid 2 mg/ml Solution for Infusion

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other side effects include:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Uncommon side effects (may affect up to 1 in 100 people):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• blurred vision</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Uncommon side effects (may affect up to 1 in 100 people):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Not known (frequency cannot be estimated from the available data):</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• changes in colour vision, difficulty in seeing detail</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>• Serotonin syndrome: risks of use with monoamine oxidase inhibitors or following consumption of tyramine-rich foods.</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Statements in the SPC / PIL as follows:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Contraindications in Section 4.3 of the SPC,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Warnings in Section 4.4 of the SPC,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Interactions with other medicinal products and other forms of interactions in Section 4.5.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• What you need to know before you are given Linezolid Infusion in Section 2 of the PIL.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>In the PIL the following wording is used:</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN LINEZOLID INFUSION</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>You should not be treated with Linezolid Infusion:</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 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 may be used to treat depression or Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Tell your doctor if you are taking or have taken within the last 2 weeks</strong> the following medicines because Linezolid Infusion must not be taken if you are already taking these medicines or have taken them recently. (See also Section 2 “You must not be given Linezolid Infusion”).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• monoamine oxidase inhibitors (MAOIs for example phenelzine, isocarboxazid, selegiline, moclobemide). These may be used to treat depression or Parkinson’s disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Linezolid Infusion with food and drink</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>
## Linezolid 2 mg/ml Solution for Infusion

### UK/H/5511/001/DC

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risks</strong></td>
<td>This is because this medicine may react with a substance called tyramine which is naturally present in some food and drinks and can cause an increase in your blood pressure. If you develop a throbbing headache after eating or drinking, tell your doctor or pharmacist immediately</td>
<td></td>
</tr>
<tr>
<td><strong>Convulsions</strong></td>
<td>Statements in the SPC / PIL as follows:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>• Warning in Section 4.4 of the SPC, Undesirable effects in Section 4.8 of the SPC.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Warning in Section 2 of the PIL, Possible side effects in Section 4 of the PIL.</td>
<td></td>
</tr>
</tbody>
</table>

In the PIL the following wording is used:

**2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN LINEZOLID INFUSION**

Talk to your doctor, pharmacist or nurse before you are treated with Linezolid Infusion if you:

• have a history of seizures

**4. POSSIBLE SIDE EFFECTS**

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

• fits or seizures have been reported with Linezolid Infusion. You should let your doctor know if you experience agitation, confusion, delirium, rigidity, tremor, incoordination and seizure while also taking antidepressants known as SSRI’s (see Section 2 “You must not be given Linezolid Infusion”).

**Other side effects include:**

**Uncommon side effects (may affect up to 1 in 100 people):**

• convulsions

**Increased risk of fatal outcome in patients with catheter related infections**

Statements in the SPC as follows:

• Precaution in Section 4.4

**Long term use (use of linezolid for more than 28 days)**

Statements in the SPC/PIL as follow:

Posology and method of administration in Section 4.2 of the SPC

In the PIL the following wording is used:

**3. HOW TO USE LINEZOLID INFUSION**

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.
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
</table>
| **Important identified risks** | periods longer than 28 days. Your doctor will decide how long you should be treated. While you are taking Linezolid Infusion, your doctor should  
- perform regular blood tests to monitor your blood count  
- monitor your eyesight if you take Linezolid Infusion for more than 28 days. | |

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important potential risks</strong></td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

| Important missing information | |
|-------------------------------| |
| • Exposure during pregnancy and lactation  
• Use in renal impairment  
• Use in hepatic impairment | |

### IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

### V User consultation
A user consultation with target patient groups on the package leaflet has been performed on the basis of two bridging reports, making reference to package leaflets for Linezolid Teva 2 mg/ml Solution for infusion (DK/H/2079/001/DC) and Ciprofloxacin 2mg/ml solution for infusion, which have both been user-tested. The first bridging report compared the content of the proposed package leaflet with the leaflet for Linezolid Teva 2 mg/ml Solution for Infusion. The second bridging report compared the layout of the proposed package leaflet with the leaflet for Ciprofloxacin 2 mg/ml Solution for Infusion. The bridging reports submitted by the applicant are acceptable.
VI Overall conclusion, benefit/risk assessment and recommendation
The quality of this product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The use of linezolid is well-established and the application includes an adequate review of published non-clinical and clinical data concerning the recognised efficacy and acceptable safety of linezolid. Bioequivalence studies were not necessary to support this application for an aqueous parenteral product, containing the same active substance as the reference product. Comparative physico-chemical characteristics have been provided for the proposed product versus the reference product, and pharmaceutical equivalence has been shown. The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), package leaflet and labelling are satisfactory, in-line with current guidelines and consistent with the reference product. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and package leaflet for this product are available on the Medicines and Healthcare products Regulatory Agency website.

The currently approved labels are listed below:
Each ml contains 2 mg Linezolid
Linezolid 600 mg/300 ml
Excipients: Glucose monohydrate, Sodium citrate, Citric acid anhydrous, Hydrochloric acid and sodium hydroxide for pH adjustment. Water for injections.
See leaflet for further information.

For intravenous use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Use only if the solution is clear, without visible particles and the seal is intact. Discard unused portion. Do not freeze. Store in the original package until ready to use in order to protect from light. After opening the product should be used immediately.

PL 36780/0001

Marketing Authorisation Holder:
Infomed Fluids S.R.L.
50 Theodor Paillady blvd. District 3
032286 Bucharest, Romania

LOT: EXP:
LINEZOLID 2 mg/ml Solution for Infusion

Each ml contains 2 mg Linezolid
Linezolid 600 mg/300 ml
Excipients: Glucose monohydrate, Sodium citrate, Citric acid anhydrous, Hydrochloric acid and sodium hydroxide for pH adjustment, Water for injections.
See leaflet for further information.
For intravenous use.

PL 36780/0001
Linezolid 2 mg/ml Solution for Infusion

Linezolid

10 bags of 300 ml

Each ml contains 2 mg Linezolid
Linezolid 600 mg/300 ml

Excipients: Glucose monohydrate, Sodium citrate, Citric acid anhydrous, Hydrochloric acid and Sodium hydroxide for pH adjustment, Water for injections. See leaflet for further information.

For intravenous use.

Read the package leaflet before use.

Keep out of the sight and reach of children.

Do not mix with other medicinal products.

Use only if the solution is clear, without visible particles and the seal is intact.

Discard unused portion. Do not freeze. Store in the original package until ready to use in order to protect from light.

After opening the product should be used immediately.

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

PL 36780/0001

Marketing Authorisation Holder: Infamed Flans S.R.L.
50 Theodor Pallady Blvd., District 3,
032260 Bucharest, Romania
Tel: +40 21 345 02 22
Fax: +40 21 345 31 85
E-mail: office@infamedfluids.ro

Infamed Fluids®
Linezolid 2 mg/ml Solution for Infusion

Linezolid

25 bags of 300 ml

Each ml contains 2 mg Linezolid
Linezolid 600 mg/300 ml

Excipients: Glucose monohydrate, Sodium citrate, Citric acid anhydrous, Hydrochloric acid and sodium hydroxide for pH adjustment, Water for injections. See leaflet for further information.

For intravenous use.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Do not mix with other medicinal products.
Use only if the solution is clear, without visible particles and the seal is intact.
Discard unused portion. Do not freeze. Store in the original package until ready to use in order to protect from light.
After opening the product should be used immediately.
Any unused product or waste material should be disposed of in accordance with local requirements.

PL 36780/0001

Marketing Authorisation Holder: Infomed Fluids S.R.L.
50 Theodor Pallady Blvd., District 3,
032266 Bucharest, Romania
Tel: +40 21 349 02 22
Fax: +40 21 349 33 85
E-mail: office@infomedfluids.ro

POM
Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report
(Type II variations, PSURs, commitments)

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/non approval</th>
<th>Assessment report attached Y/N (version)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>