

Part VI. SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. Elements for Summary Tables in the EPAR

VI.1.1. Summary Table of Safety Concerns

Table 68. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Myelosuppression Lactic acidosis Peripheral and optic neuropathy Serotonin syndrome Convulsions Mitochondrial toxicity Pseudomembranous colitis Long-term Use
Important potential risks	Increased risk of fatal outcome in subsets of patients with CRI, especially those with Gram negative organisms
Missing information	Pregnancy and lactation Use in Severe Renal Insufficiency Use in Hepatic Insufficiency

VI.1.2. Table of Ongoing and Planned Studies in the Post-Authorisation Pharmacovigilance Development Plan

No imposed mandatory additional pharmacovigilance activities, or required additional pharmacovigilance activities (i.e., categories 1 to 3) are ongoing or planned for linezolid.

VI.1.3. Summary of Post-Authorisation Efficacy Development Plan

There are no post authorisation efficacy studies planned or ongoing.

VI.1.4. Summary Table of Risk Minimisation Measures

Table 69. Summary of Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
Myelosuppression	SmPC Sections 4.4 and 4.8: See Annex 2 for current SmPC.	None.
Lactic acidosis	SmPC Sections 4.4 and 4.8: See Annex 2 for current SmPC.	None.
Peripheral and optic neuropathy	SmPC Sections 4.4 and 4.8: See Annex 2 for current SmPC.	None.
Serotonin syndrome and potential for increased blood pressure (potential to inhibit monoamine oxidase)	SmPC Sections 4.3, 4.4, 4.5 and 4.8: See Annex 2 for current SmPC.	None.
Convulsions	SmPC Sections 4.4 and 4.8: See Annex 2 for current SmPC.	None.
Mitochondrial toxicity	SmPC Section 4.4: See Annex 2 for current SmPC.	None.

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Table 70. Important Identified Risks

Risk	What is Known	Preventability
<p>Damage to the nerves in hands and feet (peripheral neuropathy) and</p> <p>Vision problems resulting from damage to the nerve that carries visual information from the eye to the brain. (optic neuropathy)</p>	<p>Damage to the nerves in hands and feet, a condition known as peripheral neuropathy, has been reported in patients treated with linezolid, primarily when the duration of therapy is longer than the maximum recommended duration of 28 days.</p> <p>Vision problems, a condition known as optic neuropathy, have been reported in patients treated with linezolid, primarily in those patients treated for longer than the maximum recommended duration of 28 days. In cases of vision loss, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with linezolid for less than 28 days.</p>	<p>Tell your doctor or another healthcare professional immediately if you develop tingling, numbness of hands/feet, decreased strength or difficulties in the way you walk, run or step.</p> <p>Tell your doctor or another healthcare professional immediately if you have problems with your vision such as blurred vision, changes in color vision, difficulty in seeing detail or if your field of vision becomes restricted.</p>
<p>Development of fast heart rate, confusion, abnormal sweating, hallucinations, involuntary movements chills and shivering) (Serotonin syndrome</p>	<p>Serotonin syndrome, including some fatal cases, are associated with linezolid use in patients also receiving drugs to treat depression such as serotonin re-uptake inhibitors (SSRIs), tricyclic Antidepressants, serotonin 5-HT1 receptor agonists (triptans), bupropion and buspirone. Other medications include meperidine (Demerol).</p>	<p>Tell your doctor or another healthcare professional if you are taking:</p> <ul style="list-style-type: none"> • 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. • The list is not complete and several other classes of drugs can determine similar events. <p>Inform your doctor if you are taking other drugs concurrently and refer to the relevant section of the PIL for more information.</p> <p>Tell your doctor or another healthcare professional immediately if you develop any of the following symptoms: hallucinations, unusual restlessness, loss of coordination, fast heartbeat, severe dizziness, sweating, shaking/shivering, unexplained fever, twitchy muscles, or</p>

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Table 70. Important Identified Risks

Risk	What is Known	Preventability
		severe nausea/vomiting/diarrhea.
Fits or seizures (convulsions)	Fits or seizures (convulsions) have been reported in patients when treated with linezolid. In some of these cases, a history of seizures or risk factors for seizures or factors that make the chance of getting seizures greater were reported.	Tell your doctor or another healthcare professional immediately if you have a previous history of seizures, a family history of seizures, a history of brain infection, or if you have fits or seizures while taking linezolid.
Cell dysfunction (Mitochondrial toxicity)	Mitochondrial toxicity is a condition in which the mitochondria (a component of human cells) don't work as well as normal. This may cause risks such as myelosuppression, lactic acidosis, and neuropathies (damage to nerves in the hands or feet, damage to the nerve in the eye that carries visual information to the brain).	See the following risks described above: myelosuppression, lactic acidosis, and neuropathies.
Inflammation of the colon Pseudomembranous Colitis (PMC)	Pseudomembranous colitis is characterized by diarrhea, abdominal pain, and fever and can occur with most antibiotics. Complications from this disorder can be life threatening. It is caused by an excessive growth of bacteria that this antibiotic does not affect. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. Pseudomembranous colitis can occur very rarely.	Healthcare professional immediately if you develop gastrointestinal symptoms ranging from nausea and abdominal pain to severe diarrhea during or after linezolid administration.
Long-term use	Numbness, tingling or blurred vision have been reported by patients who have been given Linezolid for more than 28 days. The maximum treatment duration is 28 days. The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established. Also see the important risks described above, which are more likely to occur with long term use: myelosuppression, lactic acidosis, neuropathies, mitochondrial toxicity, and pseudomembranous colitis for additional information.	See the following important risks described above: myelosuppression, lactic acidosis, neuropathies, mitochondrial toxicity and pseudomembranous colitis.

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Table 71. Important Potential Risks

Risk	What is Known
Increased risk of fatal outcome in subsets of patients with catheter-related infections, especially those with a particular class (Gram negative) of organisms	Catheter is a flexible plastic tube inserted into the body for several purposes such as for giving drugs or fluids. However, bacteria can also get into the body through the catheter. An increased risk of death was observed in patients treated with linezolid who had catheter-related infections. Linezolid is not approved for the treatment of catheter-related bloodstream infections or catheter-site infections.

Table 72. Missing Information

Risk	What is Known
Women who are pregnant or breastfeeding	The effect of linezolid in pregnant women is not known. Therefore it should not be taken in pregnancy unless advised by your doctor. Tell your doctor if you are pregnant, think you may be pregnant or are trying to become pregnant. You should not breast-feed when taking linezolid because it passes into breast milk and could affect the baby.
Use in severe Renal Insufficiency	Although no dose adjustment is required, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.
Use in Hepatic Insufficiency	Although no dose adjustment is required, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

VI.2.5. Summary of Risk Minimisation Measures by Safety Concern

There is no additional risk minimisation activity for the identified or potential risks for linezolid.

VI.2.6. Planned Post-Authorisation Development Plan

There are no post-authorisation efficacy studies planned or ongoing.

VI.2.7. Summary of Changes to the Risk Management Plan Over Time

Major changes to the Risk Management Plan over time are shown in Table 73 below.

Table 73. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
1.0	March 2007	Important Identified Risks: Myelosuppression Lactic acidosis Peripheral and optic neuropathy Serotonin syndrome Convulsions Important Potential Risks: Increased risk of fatal outcome in subsets of patients	Original RMP

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Table 73. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
		with CRI, especially those with Gram negative organisms Other: Monitoring for cardiac effects Missing information: Long-term use Pregnancy and lactation	
2.0	June 2008	Same as previous version	Provide updated information up to 30 April 2008 as part of routine review in line with PSUR submissions
3.0	January 2009	Same as previous version	Document updated based on Assessment Report for PSURs 9 and 10
4.0	June 2009	Same as previous version	Provide updated information up to 30 April 2009 as part of routine review in line with PSUR submissions
5.0	June 2010	Mitochondrial toxicity added as an important potential risk.	Provide updated information up to 17 April 2010 as part of routine review in line with PSUR submissions
6.0	June 2011	Mitochondrial toxicity removed as an important potential risk and added as an important identified risk.	Provide update information up to April 2011 as part of the routine review in line with PSUR submission. This version was provided and approved within the linezolid UK/H/5156/001-003/DC procedure.
7.0	October 2013	Monitoring for cardiac effects was removed as "other risk."	Submitted as part of the Linezolid Pfizer DCP UK/H/5515/001-003/DC.
7.1	July 2014	Peripheral neuropathy and optic neuropathy merged into one important identified risk: Peripheral and optic neuropathy. Pseudomembranous colitis added as new important identified risk. Long-term use moved from missing information to important identified risk. Use in severe renal insufficiency and Use in hepatic insufficiency added as new missing information.	Updated as part of the Linezolid Pfizer DCP UK/H/5515/001-003/DC.

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Table 73. Major Changes to the Risk Management Plan Over Time

Version	Date	Safety Concerns	Comment
7.2	October 2014	No content change. Minor update to Section VI.2 – Elements for a Public Summary.	Approved during the Linezolid Pfizer DCP UK/H/5515/001-003/DC.
6.1	June 2015	Conversion to the current RMP format. Content aligned with the linezolid (Dual Brand) RMP version 7.2 (DCP UK/H/5515/001-003/DC). In the current version 6.1, reference is made to the Zyvox SmPC rather than the linezolid Pfizer SmPC cited in version 7.2.	Document updated as part of the Response to RFI received with Preliminary Assessment Report dated 10 th April 2015 for PSURs 13 and 14.
7.3	November 2015	No content change.	Administrative update to harmonise the RMP across the Linezolid licences to have one core RMP for the Linezolid molecule. Consolidation between the Dual Brand and Main Brand RMPs.
8.0	April 2016	Part II SIII updated with comprehensive 24 - CT dataset. Final PV additional activities A5951110 and Mortality Review Board (MRB) presented.	Provide updated information up to 15 December 2015 as part of routine review in line with PSUR submissions
8.1	October 2016	No content change. Annex 7 updated.	Document updated as per MHRA communication; email dated 06 th October 2016.

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