VI.2. Elements for a Public Summary

VI.2.1. Overview of Disease Epidemiology

Lung infections including those resulting from normal social contact in the community, those resulting from hospitalization, and those resulting from being on a breathing machine.

Pneumonia contracted outside of a hospital (community-acquired pneumonia [CAP]) is a leading cause of disease and death, worldwide. The incidence of CAP varies widely between different groups of people. However, most studies have shown that this type of pneumonia occurs more frequently during certain seasons, at a higher rate in men, and at a higher rate in persons at the extremes of age (young and old).

Hospital acquired lung infection, otherwise defined as nosocomial pneumonia, refers to any lung infection contracted by a patient in a hospital at least 48 hours after being admitted. It is usually caused by a bacterial infection, rather than a virus. Hospital acquired lung infection is the second most common hospital infection and accounts for 15-20% of the total. Breathing machine-associated lung infection is a sub-type of hospital acquired lung infection, which occurs in people who are receiving mechanical ventilation. Studies show that the mortality with breathing machine-associated lung infection ranges from 3-17%.

Skin and tissues directly under the skin infections complicated by other factors such as treatment resistance and other medical conditions.

Complicated skin and tissues directly under the skin infections are a group of disorders that include infections involving abnormal skin or wounds, those occurring in a person with a weaker immune system (lower ability to fight infection), or requiring surgical intervention. These also include infections of diseased skin, injury or bite-related wounds, infections where surgery was performed, and long-term wound infections (such as diabetic foot and pressure sores). They are among the most common infections treated in a hospital setting and may be caused by bacteria that do not respond to some antibiotics (drug resistant infections).

VI.2.2. Summary of Treatment Benefits

Linezolid is an oxazolidinone class antibacterial used in adults for the treatment of the following infections caused by susceptible gram positive bacteria:

- Nosocomial Pneumonia caused by Staphylococcus aureus (methicillin susceptible and resistant isolates) or *Streptococcus pneumoniae*.

- Community Acquired Pneumonia (CAP) caused by *Streptococcus pneumoniae* including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin susceptible isolates).

- Complicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin susceptible and resistant isolates), *Streptococcus pyogenes*, or *Streptococcus agalactiae*.

- Uncomplicated skin and skin structure infections caused by *Staphylococcus aureus* (methicillin susceptible isolates only) or *Streptococcus pyogenes*, and Vancomycin resistant *enterococcus faecium* infections including cases with concurrent bacteremia.

- Complicated Skin and Skin structure Infections (cSSSI).

VI.2.3. Unknowns Relating to Treatment Benefits

Of 6,037 patients treated with linezolid in clinical phases, 978 (16.1%) were 65-74 yrs. and 951 (15.7%) were 75 yrs. or older. No major differences in treatment benefit were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between elderly and younger patients.

In addition pharmacokinetic data indicate that the total clearance of linezolid is not influenced by race or gender and therefore the treatment benefits in these patient subgroups would be expected to be similar without dose adjustments.

There are no unknowns relating to treatment benefits with linezolid other than benefits in pregnant or lactating patients or in those patients with hepatic insufficiency or severe renal insufficiency.

Summary of Safety Concerns

Table 70. Important Identified Risks

Risk	What is Known	Preventability
Reduction in the number of cells in the blood which maintain immune function, carry oxygen, and are responsible for normal blood clotting (Myelosuppression)	Myelosuppression has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the level of the affected cell type has risen toward pre-treatment levels. Discontinuation of linezolid should be considered in patients who develop or have worsening myelosuppression. In case of myelosuppression, patients are more prone to develop infections. Although these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days, this has also been reported in patients receiving shorter courses of therapy.	While you are taking linezolid, your doctor should perform regular blood tests to monitor your blood count if you • receive linezolid for longer than two weeks, • have pre-existing myelosuppression, • are receiving drugs that produce bone marrow suppression while taking linezolid, or • have received or are receiving or concomitant antibiotic therapy for a long-term infection. Tell your doctor or another healthcare professional immediately if bruising , bleeding or anaemia occurs
Development of recurrent nausea and vomiting, abdominal pain, over breathing)	Patients experiencing repeated episodes of nausea and vomiting may have a condition known as lactic acidosis when taking linezolid. Although these reports have primarily been in patients	Tell your doctor or another healthcare professional immediately if you develop recurrent nausea or vomiting,

Table 70. Important Identified Risks

Risk	What is Known	Preventability
(Lactic acidosis)	treated for longer than the maximum recommended duration of 28 days, this affect has also been reported in patients receiving shorter courses of therapy.	abdominal pain or over breathing.

Table 70. Important Identified Risks

Risk	What is Known	Preventability
Damage to the nerves in hands and feet (peripheral neuropathy) and Vision problems resulting from damage to the nerve that carries visual information from the eye to the brain. (optic neuropathy)	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. 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.	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. 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.
Development of fast heart rate, confusion, abnormal sweating, hallucinations, involuntary movements chills and shivering) (Serotonin syndrome	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).	Tell your doctor or another healthcare professional if you are taking: • 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. Inform your doctor if you are taking other drugs concurrently and refer to the relevant section of the PIL for more information. 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,

Table 70. Important Identified Risks

Risk	What is Known	Preventability
		shaking/shivering, unexplained fever, twitchy muscles, or 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.

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.2.4. Summary of Risk Minimisation Measures by Safety Concern

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

VI.2.5. Planned Post-Authorisation Development Plan

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

VI.2.6. 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:	Original RMP

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

Version	Date	Safety Concerns	Comment
		Increased risk of fatal outcome in subsets of patients 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.

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 10th 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