Risk Management Plan Summary

For

Linezolid

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Nosocomial pneumonia (NP):

NP (hospital acquired pneumonia) is most common in elderly patients; however, patients of any age may be affected. It is common in the intensive care units (ICU) and outside ICU. In the recent studies, the frequency was reported as 6.8–27%. In a study in European ICUs, ICU-acquired pneumonia accounted for 46.9% of nosocomial infections. The risk of pneumonia is increased in the intubated (insertion of a tube via oral cavity) patients receiving mechanical ventilation (MV) (artificial ventilation) and the ventilator associated pneumonia (VAP) (a type of pneumonia which occurs in people who are receiving mechanical ventilation) frequencies varied between 7–70% in different studies. The progress in patients with hospital acquired pneumonia depends primarily on preexisting conditions and host defenses, with early-onset disease having a better prognosis. NP is also associated with high deaths in ICUs. The death rate reaches to 20–50%, and also NP caused by high-risk organisms which cause disease is associated with higher death rates.

Community acquired pneumonia (CAP):

CAP (pneumonia acquired from social contact) is a relatively frequent infectious illness which causes diseased state worldwide. The reported frequency rates of radiographically (imaging technique that uses electromagnetic radiation other than visible light, especially X-rays, to view the internal structure of a human body) confirmed CAP in different populations have varied between 1.3 and 11.6 cases per 1,000 persons. The frequency of the condition is age-related with the highest rates in the very young and very old. There is no optimal therapy for community-acquired pneumonia (CAP). CAP may be treated with a single antibiotic therapy or a combination therapy.

Complicated skin and soft tissue infections (cSSTI):

Skin and soft tissue infections (SSTIs) are common in outpatient clinic and emergency department visits and include a wide variety of infections of the various layers of skin, fascia (structure of connective tissue that surrounds muscles) and muscle. SSTIs usually result from traumatic, surgical or healthcare-related skin break down with secondary infection with microorganisms.

Among hospitalized or critically ill patients, several studies have shown that about 4.3%-10.5% of septic (infected) episodes are caused by SSTIs. In large database study on skin related conditions in the intensive care unit (ICU), only 0.4% of all ICU admissions had SSTIs, and about 60% of which were necrotizing fasciitis (a severe bacterial infection of the tissues that line and separate muscles, that causes extensive tissue death). Another two studies, including only "superficial" and "deep and/or healthcare- associated" infections, have shown that about 2.0%-5.8% of hospitalized SSTI patients are admitted to the ICU.

VI.2.2 Summary of treatment benefits

Linezolid is an antibiotic of the oxazolidinones group that works by stopping the growth of certain bacteria (germs) that cause infections. It is used to treat pneumonia (lung infection) and some infections in the skin or under the skin.

The efficacy studies were conducted for the reference product Zyvox and no studies to evaluate the expected benefit were performed for Linezolid Accord, considering its similarity to Zyvox.

VI.2.3 Unknowns relating to treatment benefits

. There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old) to establish dosage recommendations and also there are no adequate data from the use of linezolid in pregnant women.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Decreased blood count (Myelosuppression)	Linezolid can cause reduction in the numbers of cells in the blood.	By performing regular blood tests to monitor blood count while on linezolid
Metabolic condition in which lactic acid builds up in the bloodstream faster than it can be removed due to drop in the oxygen levels in body and symptoms will include recurrent nausea and vomiting, abdominal pain and over breathing (Lactic acidosis)	Linezolid can lead to lactic acidosis (symptoms include recurrent nausea and vomiting, abdominal pain, overbreathing).	Inform doctor immediately in case of recurrent nausea or vomiting, abdominal pain or over breathing.
Damage to the nerves in hands and feet (Peripheral neuropathy)	Peripheral neuropathy, 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. There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications	By avoiding treatment longer than recommended duration of 28 days and by avoiding linezolid in patients currently taking or who have recently taken the treatment for tuberculosis.

Risk	What is known	Preventability
	for the treatment of tuberculosis.	
Damage to the nerves in eyes (Optic neuropathy)	Blurred vision has been reported by patients who have been given linezolid for more than 28 days.	By avoiding treatment longer than recommended duration of 28 days. If during treatment problems with vision such as blurred vision, changes in colour vision, difficulty in seeing detail or field of vision becomes restricted, inform doctor immediately.
Symptoms that include fast heart rate, confusion, abnormal sweating, hallucinations, involuntary movements chills and shivering (Serotonin syndrome) and potential for increased blood pressure (potential to inhibit monoamine oxidase)	Linezolid can cause serotonin syndrome (symptoms include fast heart rate, confusion, abnormal sweating, hallucinations, involuntary movements chills and shivering).	Inform doctor of concurrent use of certain antidepressants known as tricyclics or SSRIs (selective serotonin reuptake inhibitors). There are many of these, including amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, sertraline.
Convulsions	Linezolid can lead to convulsions.	Tell doctor about history of seizures and if you experience agitation, confusion, delirium, rigidity, tremor,

Risk	What is known	Preventability
		incoordination and seizure while also taking antidepressants
Mitochondrial toxicity	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.	By avoiding treatment longer than recommended duration of 28 days.
Severe diarrhoea containing blood and/or mucus (Antibiotic associated colitis including Pseudomembranous colitis)	Linezolid can lead to severe diarrhoea containing blood and/or mucus (Pseudomembranous colitis).	In case of severe diarrhoea containing blood and/or mucus (antibiotic associated colitis including pseudomembranous colitis) during treatment, stop taking Linezolid immediately and consult doctor. In this situation, one should not take medicines that stop or slow bowel movement.
Long term-use of more than 28 days	Linezolid over 28 days is associated with an increased risk of decreased blood count	While the patient is taking Linezolid, doctor should perform regular blood tests to

Risk	What is known	Preventability
	(myelosuppression), mitochondrial dysfunction, lactic acidosis and damage to nerves in the peripheral nervous system (neuropathies).	monitor patient's blood count. Doctor should monitor patient's eyesight if he/she is taking Linezolid for more than 28 days.

Important potential risks

Risk	What is known
Increased risk of death (fatal outcome) in subsets of patients with catheter related infections, especially those with gram negative organisms	An increased risk of death was observed in patients treated with linezolid who had catheter-related infections especially those caused by bacteria known as gram negative bacteria. 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 at the same time.

Missing information

Risk	What is known
Limited information on the use in children and adolescent	Linezolid is not normally used to treat children and adolescents (under 18 years old).
Limited information on the	The effect of linezolid in pregnant women is not known.

Risk	What is known
use in pregnant and lactating females	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 breastfeed when taking linezolid because it passes into breast milk and could affect the baby.
Use in Severe Liver failure (severe hepatic insufficiency)	There are limited clinical data and it is recommended that linezolid should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.
Use in Kidney failure (Use in renal insufficiency)	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.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

No studies planned.

VI.2.7 Summary of changes to the risk management plan over time

Not Applicable