VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Nosocomial pneumonia

Nosocomial, or hospital acquired, pneumonia (inflammation of the lungs) is a lower respiratory tract infection that was not present on admission to the hospital. Usually, infections occurring 48 hours or more after admission are considered hospital acquired.[i] Nosocomial pneumonia is the second most common cause of hospital acquired infection and has a mortality rate of 20% to 50%.[ii] It is one of the most common diagnoses made in medical and surgical intensive care units (ICUs) and is common in patients undergoing mechanical ventilation (assisted or controlled ventilation using mechanical devices that cycle automatically to generate airway pressure). Nosocomial pneumonia also occurs in patients in the general hospital wards who are not receiving mechanical ventilation.[iii] 90% of these infections are bacterial.

Community acquired pneumonia (CAP)

CAP is an infection from organisms found in the community rather than in the hospital or nursing home. The infection begins outside the hospital or is diagnosed within 48 hours after admission to the hospital in a person who has not been in a long-term care facility for 14 days or more before admission.[ii]
CAP is an important cause of deaths and occurrence of diseases worldwide. It is usually caused by a bacterial infection, rather than a virus.[iv]
CAP usually results from inhalation or aspiration of pulmonary pathogenic organisms into a lung segment or lobe.[v]

Complicated skin and soft tissue infections (cSSTIs)

Skin and soft tissue infections (SSTIs) are common, and cSSTIs are the more extreme end of this clinical condition, covering a range of clinical presentations such as infections far below the skin surface, a need for surgical intervention, the presence of systemic signs of infection in the bloodstream, the presence of undesired result of complication, decreased number of white blood cells, inadequate blood supply to the tissue, death of a group of the cells, burns and bites. *Staphylococcus aureus* is the commonest cause of SSTI across all continents. Susceptible individuals include diabetics and elderly.[vi]

VI.2.2 Summary of treatment benefits

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 anaerobic micro-organisms. Linezolid selectively inhibits bacterial protein synthesis via a unique mechanism of action.

Based on the available data from studies in patients and clinical experience of several years, linezolid represents an effective drug in the treatment of nosocomial pneumonia, community acquired pneumonia and complicated skin and soft tissue infections.

If administered as indicated in the Summary of Product Characteristics and taking into account the contraindications, the warnings and precautions for use, linezolid can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Myelosuppression (*Severe reduction in blood cells which can cause weakness, bruising or make infections more likely*)	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 are common side effects of linezolid (may affect up to 1 in 10 people). Reduction in the numbers of certain cells in the blood which may affect the ability to fight infection is uncommon side effect of linezolid (may affect up to 1 in 100 people).	Talk to your doctor before taking Linezolid Teva if you: • Bruise and bleed easily, • Are anaemic, • Are prone to getting infections. While you are taking Linezolid Teva, your doctor should perform regular blood tests to monitor your blood count.
Increased risk of fatal outcome in subsets of patients with catheter related infections (CRI), especially those with Gram negative organisms (*Increased risk of deaths in patients with infections related to catheters*)	In seriously ill patients with infections related to catheters inserted into vessels an increased number of deaths in patients taking linezolid in comparison to therapy with vancomycin/ dicloxacillin/ oxacillin was found.	Linezolid therapy should only be started in hospital.
Lactic acidosis (*Low pH in body tissues and blood*)	Lactic acidosis has been reported (frequency cannot be estimated from the available data). Symptoms include recurrent nausea and vomiting, abdominal pain, over-breathing.	Tell your doctor or pharmacist **immediately** if you notice any of these side effects during your treatment with Linezolid Teva: • Recurrent nausea or vomiting • Abdominal pain • Over-breathing.
Mitochondrial toxicity (*Damaged or significantly reduced number of mitochondria of a body's cells*)	Side effects such as low pH in body tissues and blood, low number of red blood cells, problems with vision (blurred vision, changes in colour vision, difficulty in seeing detail or restricted field of vision), and disorder of the nerves which can cause weakness, tingling or numbness, may develop as a result of mitochondrial damage.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the leaflet. 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.
Serotonin syndrome (*Unexplained fever with faster breathing or heart rate, sweating, muscle*	Serotonin syndrome (symptoms include fast heart rate, confusion, abnormal sweating, hallucinations, involuntary movements chills and shivering)	Linezolid Teva 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

Risk	What is known	Preventability
stiffness or tremor, confusion, extreme agitation or sleepiness) **and potential for increased blood pressure (potential to inhibit monoamine oxidase)**	has been reported (frequency cannot be estimated from the available data). Increased blood pressure is uncommon side effect of linezolid (may affect up to 1 in 100 people).	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? • 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, schizoaffective disorder, mental confusion or other mental problems? • Are you taking any of the following medicines? - Decongestant cold and flu medicines containing psuedoephedrine or phenylpropanolamine, - Some medicines used to treat asthma such as salbutamol, terbutaline, fenoterol, - Certain antidepressants known as tricyclics or SSRIs (selective serotonin re-uptake inhibitors). There are many of these, including amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, sertraline, - Medicines used to treat migraine such as sumatriptan and zolmitriptan, - Medicines to treat sudden, severe allergic reactions such as adrenaline (epinephrine), - Medicines which increase your blood pressure such as noradrenaline (norepinephrine), dopamine and dobutamine, - Medicines used to treat moderate to severe pain, such as pethidine, - Medicines used to treat anxiety disorders, such as buspirone. Do NOT take Linezolid Teva if you are taking or have taken within the last 2 weeks any medicines known as monoamine oxidase inhibitors (MAOIs, e.g. phenelzine, isocarboxazid, selegiline, moclobemide). These may be used to treat depression or Parkinson's disease.

Risk	What is known	Preventability
		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.
Peripheral neuropathy (*Disorder of the nerves which can cause weakness, tingling or numbness*)	Dizziness and sensations such as tingling or feeling numb are uncommon side effects of linezolid (may affect up to 1 in 100 people). Numbness or tingling have been reported by patients who have been given Linezolid Teva for more than 28 days.	If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the leaflet.
Optic neuropathy (*Problems with vision such as blurred vision, changes in colour vision, difficulty in seeing detail or restricted field of vision*)	Blurred vision is an uncommon side effect of linezolid (may affect up to 1 in 100 people). Changes in colour vision, difficulty in seeing detail or if the field of vision becomes restricted have been reported (frequency cannot be estimated from the available data). Blurred vision has been reported by patients who have been given Linezolid Teva for more than 28 days.	Tell your doctor **immediately** if during treatment you suffer from: • Problems with your vision such as blurred vision, changes in colour vision, difficulty seeing detail or if your field of vision becomes restricted. If you experience difficulties with your vision you should consult your doctor as soon as possible. Your doctor should monitor your eyesight if you take Linezolid Teva for more than 28 days.
Convulsions (*Seizures*)	Fits or seizures have been reported with Linezolid Teva.	Talk to your doctor <u>before</u> taking Linezolid Teva if you have a history of seizures. You should let your doctor know if you experience seizure while also taking antidepressants known as selective serotonin re-uptake inhibitors (SSRIs). If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in the leaflet.

<u>Important potential risks</u>

Risk	What is known (Including reason why it is considered a potential risk)
Cardiac events (*Heart events*)	Patients treated with Linezolid Teva may be at an increased risk of developing heart events.

Risk	What is known (Including reason why it is considered a potential risk)
	The exact mechanism by which linezolid may cause heart problems is not well-understood.

Missing information

Risk	What is known
Use in children	Linezolid Teva is not normally used to treat children and teenagers (under 18 years old).
Use during pregnancy	The effect of Linezolid Teva 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.
Use during breast-feeding (lactation)	You should not breast-feed when taking Linezolid Teva because it passes into breast milk and could affect the baby.
Long-term use	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.

VI.2.5 Summary of additional risk minimisation measures by safety concern

No additional risk minimisation measures are proposed.

VI.2.6 Planned post authorisation development plan (if applicable)

Not applicable.

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

Not applicable. No version of Teva's linezolid RMP has been approved yet.

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[i] McEachen R, Campbell GD. Hospital-acquired pneumonia: Epidemiology, etiology, and treatment. Infectious Disease Clinics Of North America 12(3). 1998; 761-779.

[ii] Chestnutt MS, Prendergast TJ. Current Medical diagnosis and treatment (42nd Edition). New York: Lange MedicalG roups/McGRAW-Hill. 2003; pg 246-256.

[iii] http://emedicine.medscape.com/article/234753-overview#aw2aab6b5; accessed on 04 July 2013

[iv] Mandell GL, Bennet JE, Dolin R et al. Mandell's principles and practice of infection Diseases 6th Edition; 2004; Curchill Livingstone. ISBN 0-443-06643-4.

[v] Cilloniz C, Ewig S, Ferrer M, et al. Community acquired polymicrobial pneumonia in the intensive care unit: aetiology and prognosis. *Crit Care*. Sep 14 2011;15(5):R209.

[vi] Dryden MS. Complicated skin and soft tissue infection. J Antimicrob Chemother**.** 2010 Nov;65 Suppl 3:iii35-44. doi: 10.1093/jac/dkq302.