## VI.2 Elements for a public summary

### *VI.2.1 Overview of disease epidemiology*

**Nosocomial pneumonia (NP)** – is hospital-acquired pneumonia (HAP) and refers to any pneumonia contracted by a patient in a hospital at least 48–72 hours after being admitted. It is usually caused by a bacterial infection, rather than a virus. Nosocomial pneumonia is the second most common hospital-acquired infection and the leading infection in critical care units. According to data of the European point-prevalence study EPIc, nosocomial pneumonia accounts for 47% of all intensive care units-acquired infections. In a large survey of 27 intensive care units in nine European countries the overall prevalence of NP was 8.1% (ranging from 0% to 24.5% among participating intensive care units)[1].
Nosocomial pneumonia can increase intensive care units length of stay by approximately 12 days. Methicillin resistant Staphylococcus aureus (MRSA) (bacteria resistant also to some newer antibiotics because they do not work in the lungs) now accounts for a large proportion of all cases of NP[2].

**Community acquired pneumonia (CAP)** - is one of diseases in which individuals who have not recently been hospitalized develop an infection of the lungs (pneumonia). People most at risk are older than 65 or younger than 2 years of age, or already have health problems. Community-acquired pneumonia (an infection of the lungs that is caught outside of hospital) is a common disease, with an annual incidence of 5 to 11 cases per thousand adults.[3]

***Complicated skin and soft tissue infections***
A skin and soft tissue infection are bacterial infections of the skin and associated tissues. The complicated category includes infections either involving deeper soft tissue or requiring significant surgical intervention, such as infected ulcers, burns, and major abscesses (swelling filled with pus) or superficial infections or abscesses in an anatomical site, such as the rectal area, where the significant underlying disease state that complicates the response to treatment. Skin infections are highly diverse in their causes, manifestations and severity. Severity ranges from minor superficial lesions to invasive (tending to spread prolifically and undesirably or

harmfully), fulminant (severe and sudden in onset) and even lethal (deadly) infections. It is difficult to make an assessment of the exact frequency of skin infections probably because of variable presentation. Among hospitalized patients there were 7% to 10 % patients with skin infections.[4]

### *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. Linezolid's mechanism of action differs from those of other antibiotic classes. In vitro studies with clinical isolates indicate that linezolid is usually active against organisms which are resistant to one or more other classes of antimicrobial agents. The medicine can only be obtained with a prescription.
With linezolid the following disease can be treated: pneumonia (infection of the lungs) acquired outside the hospital and acquired in the hospital, complicated skin and underneath the skin, including muscles (this is called 'soft tissue') caused by resistant Gram-positive organisms (kind of bacteria), especially Methicillin resistant Staphylococcus aureus MRSA.
A number of randomized controlled trials comparing linezolid to comparator drugs have been performed in adults and children for a number of clinical indications. These are summarized below: Linezolid was similar to comparator drug for the empiric treatment of nosocomial pneumonia in a 4 controlled studies.[5]
In a 3 multicenter trial, clinical cure rates for community acquired pneumonia were superior with therapy with linezolid compared with other drugs.
Results of a 4 controlled trial demonstrated similar or superior efficacy and tolerability between comparator drug and linezolid therapy for the treatment of complicated skin and skin structure infections, which included infections caused by methicillin-resistant Staphylococcus aureus (MRSA).[5]

### *VI.2.3 Unknowns relating to treatment benefits*

Linezolid has been associated with a number of serious adverse effects, especially in patients treated for more than the recommended 28 days. In particular, myelosuppression and peripheral and optic neuropathy have been of significant concern. This side effect will probably limit use of linezolid only in hospital use and not in common ambulatory use. The linezolid product information states that the safety and efficacy of linezolid for use for longer than 28 days has not been established. Linezolid should only be used for longer than the recommended 28 days if no other treatment exists. In these cases close monitoring for toxicity is required.[5]

### *VI.2.4 Summary of safety concerns*
**Important identified risks**

| **Risk** | **What is known** | **Preventability** |
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| A condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells, and platelets**.** | A condition in which bone marrow activity is decreased appears to be related to the duration of treatment (more than 10 to 14 days) Hematologic abnormalities were consistent with mild, reversible, | Preventability is possible by monitoring for early symptoms.<br><br>The doctor or pharmacist should be informed if the patient has severe unexplained bleeding or |

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| **(Myelosuppression including anaemia, leucopenia, pancytopenia and thrombocytopenia)** | duration-dependent. Elderly may be at greater risk. Decreased platelets may occur more commonly in patients with severe renal insufficiency. Patients that already have decreased blood cells have greater risk to develop these effects. Appropriate monitoring is warranted with linezolid use. Linezolid should be administered to such patients only when close monitoring of hemoglobin levels, blood counts and platelet counts is possible. If significant decreased occurs, treatment should be stopped unless it is considered absolutely necessary. In these cases it is recommended that complete blood counts should be monitored weekly. Serious anaemia was reported in patients receiving linezolid for more than 28 days. These patients more often required blood transfusion. | 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 (low red blood cells), changes in numbers of cells in the blood which may affect patient's ability to fight infection. |
| Physiological condition with persistently increased blood lactate levels (**Lactic acidosis**) | Lactate is a by-product of anaerobic respiration and is normally cleared from the blood by the liver, kidney and skeletal muscle.<br>Lactic acidosis (symptoms such as deep, rapid breathing, abdominal pain, weakness, nausea and vomiting) has been reported. Patient who developed symptoms of lactic acidosis should receive immediate medical attention. The benefits of continued use of linezolid should be weighed against the potential risks. | Preventability is possible by monitoring for early symptoms (deep, rapid breathing, abdominal pain, weakness, nausea and vomiting).<br>If the treatment is still preferred, the treatment may be continued. |
| **Damage to the nerves in hands, feet and eye** (Peripheral and optic neuropathy) | Patients may experience some form of nerve damage which may increase after 28 days of treatment. The nerve damage varies from mild tingling and altered sensation to irreversible disabling damage in the most severe cases. In the case of optic neuropathy it could progress to loss of vision. Early symptoms usually resolve or improve upon dose adjustment or discontinuation of therapy. If any patients are taking linezolid for longer than recommended 28 days, their visual function should be regularly monitored. | Preventability is possible by monitoring for early symptoms. All patients should be advised to consult the doctor as soon as possible if experience difficulties with their vision (changes in visual acuity, changes in colour vision, blurred vision or vision field defect), numbness, tingling or lag and arm weakness. |
| **A life-threatening syndrome that develops** | Cases of serotonin syndrome have been reported in patients taking | Linezolid may not be suitable for the patients who are taking |

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| **due to high levels of the chemical serotonin when linezolid is administered concomitant with drugs so–called serotonergic (**Serotonin syndrome**)** | linezolid concomitant with other medications especially in cases of serotonergic drugs, i.e.: amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, sertraline. These interactions increase the levels of the chemical serotonin. Serotonin syndrome symptoms typically occur within several hours of taking a new drug or increasing the dose of a drug the patient are already taking. Signs and symptoms include: Agitation or restlessness, confusion, rapid heart rate and high blood pressure, dilated pupils, loss of muscle coordination or twitching muscles, heavy sweating, diarrhea, headache, shivering, and goose bumps. Severe serotonin syndrome can be life-threatening. Signs and symptoms include: High fever, seizures, irregular heartbeat, and unconsciousness. | antidepressant known as tricyclics or SSRIs (selective serotonin reuptake inhibitors) for example: amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, sertraline. The doctor may decide to give linezolid to the patient but he will need to check patient's general health carefully before and during the treatment. |
| Fit - sudden, uncontrolled muscle spasms and loss of consciousness resulting from abnormal brain function (**Convulsions**) | Convulsions have been reported to occur in patients when treated with linezolid. In most of these cases, a history of seizures or risk factors for seizures was reported. | Yes, by monitoring for early symptoms. The doctor should advise the patient to inform the doctor if the patient suffer from epilepsy or seizures (fit) or a condition which makes patient likely to have convulsions (have had damage to your brain due to a stroke or other brain injury). Patient should inform the doctor if he (she) experience agitation, confusion, delirium, rigidity, tremor, incoordination and seizure while also taking antidepressants known as SSRI's. |

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| Damage of a specialized subunit within a cell that has a specific function (**Mitochondrial toxicity**) | Damage and subsequent dysfunction in mitochondria is an important factor in a range of human diseases due to their influence in cell metabolism. Linezolid inhibits mitochondrial protein synthesis. 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. | Preventability is possible by using the drug no longer than 28 days and by monitoring for early symptoms. |
| Inflammation of the large intestines associated with the use of antibiotics Antibiotic-associated diarrhea (**Pseudomembranous colitis**) | Diarrhoea, particularly if severe, persistent and/or bloody, during or after treatment with linezolid (including several weeks after treatment), may be symptomatic of Clostridium difficile-associated disease. It is an inflammation of the intestines that occurs following antibiotic treatment and is caused by toxins produced by the bacterium Clostridium difficile. Symptoms of antibiotic-associated colitis usually begin four to ten days after antibiotic treatment has begun. | Yes, by monitoring for early symptoms.<br>If patient experience inflammation of the large intestine, causing watery diarrhoea usually with blood and mucus, stomach pain and/or fever patient need to stop taking the medicine and contact a doctor immediately so that an appropriate therapy can be initiated.<br>Patient should not take medicines that stop or slow down bowel movement. |
| Long –term treatment (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. Numbness, tingling or blurred vision have been reported by patients who have been given linezolid for more than 28 days. | Yes, not to treat the patient longer than 28 days. If the doctor decided to treat patient more than 28 days he should monitor patient's eyesight. |

**Important potential risks:**

| Risk | What is known |
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| Increased risk of death in the patients with catheter, especially those with infections caused by Gram negative bacteria | According data from clinical study in seriously ill patients was seen higher mortality if infections were caused with several types of bacteria or with special kind of bacteria so-called Gram negative bacteria. In such cases treatment against Gram negative bacteria must be initiated concomitantly. |

**Missing information**

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| 1.8.2 clean | Linezolid |
| Risk Management System | film-coated tablets |

| **Risk** | **What is known** |
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| Pregnancy and breast-feeding | The effect of linezolid in pregnant women is not known. Therefore, it should not be taken in pregnancy unless advised by the doctor.<br>Linezolid passes into breast milk and could affect the baby so must not be used in breast-feeding women. |
| Severe damage or injury of the liver and kidney (Use in severe hepatic and renal insufficiency) | In severe renal insufficiency, there are limited experiences and linezolid should be used with special caution. Also, there are limited clinical data in patient with severe damage of liver. As linezolid is metabolized by non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism. |

### *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*

Not applicable. No postauthorisation studies are planned.

### *VI.2.7 Summary of changes to the Risk Management Plan over time*

Not applicable.