PUBLIC SUMMARY OF RISK MANAGEMENT PLAN (RMP)

LINEZOLID ORION 600 MG TABLETS

ORION CORPORATION

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VI.2 Elements for a Public Summary

Linezolid Orion is indicated in the treatment of nosocomial pneumonia, community acquired pneumonia and complicated skin and soft tissue infections.

VI.2.1 Overview of disease epidemiology

Pneumonia is a common lung infection caused by bacteria, virus or fungi. Its symptoms can vary from mild to severe and even life-threatening. In many cases pneumonia is a complication of respiratory infection—especially flu—but there are more than 30 different causes of the illness. Pneumonia can affect anyone, but two age groups at highest risk are small children and elderly. Other risk factors for pneumonia include chronic disease (including COPD and asthma), weakened or suppressed immune system e.g. due to HIV/AIDS, organ transplant, chemotherapy or long-term treatment with steroids.

Hospital acquired pneumonia (nosocomial pneumonia)

Some people catch pneumonia during a hospital stay for another illness. This type of pneumonia can be serious because the bacteria causing it may be more resistant to antibiotics. People who are on breathing machines (ventilators), often used in intensive care units, are at higher risk of this type of pneumonia.

Community acquired pneumonia

Community-acquired pneumonia is the most common type of pneumonia. It occurs outside of hospitals or other health care facilities.

Complicated skin and soft tissue infections

Infection of the skin and soft tissue of the skin is usually caused by bacteria, such as staphylococci or streptococci that are commonly present on the skin or inner surface of the nose or mouth of otherwise normal and healthy people. The infection develops when there is a break in the skin, such as a wound or injury, which may be minor or even unnoticed. This allows bacteria to enter the skin and grow, causing infection and swelling.

Complicated skin and soft tissue infections typically involve deep soft tissue and occur in patients with underlying disease, often requiring intravenous antibiotic therapy, surgical intervention, or both. This type of infections are among the most rapidly increasing reasons for hospitalization.

VI.2.2 Summary of treatment benefits

Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, theoxazolidinones. It works by killing bacteria or preventing their growth by interfering bacteria's protein synthesis. It is used for serious infections which are difficult to treat with other antibiotics.

The mechanism of action for linezolid is different than that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. However, cases of resistance have been reported also for linezolid.

Linezolid can be beneficial in treatment of infections caused by gram positive bacteria which are resistant for other antibiotics, especially infections caused by multiresistent staphylococci or enterococci.

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 caused by bacteria.

Linezolid should only be initiated in a hospital environment and after consultation with a relevant specialist such as a microbiologist or infectious diseases specialist.

VI.2.3 Unknowns relating to treatment benefits

Controlled clinical trials did not include patients with diabetic foot lesions, decubitus or ischaemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
Severe reduction in blood cells which can cause weakness, bruising or make infections more likely (Myelosuppression)	Severe reduction in blood cells has been reported in patients receiving linezolid. The risk of these effects appears to be related to the duration of treatment (more than 10-14 days of therapy). Elderly may be at greater risk than younger patients. Reduced number of platelets (thrombocytopenia) may occur more commonly in patients with severely insufficient kidney function.	Doctor should be informed of any current or previous problems related to blood cells e.g. easy bruising and bleeding, anaemia (low level of red blood cells), prone to get infections (can be sign of low level of white blood cells). Doctor should also be informed of any kidney problems. Some concomitant medications may also increase risk for myelosuppression therefore doctor should be informed of all other concomitant medications. Blood levels can be monitored with laboratory tests before and during treatment so that possible problems can be detected early and linezolid therapy may be discontinued.
Low pH in body tissues and blood (Lactic acidosis)	Lactic acidosis has been reported with the use of linezolid. In this condition lactic acid builds up in the bloodstream faster than it can be removed causing too low pH.	Patients who develop signs and symptoms of this condition including recurrently feeling sick or vomiting, stomach pain or hyperventilation while receiving linezolid should receive immediate medical attention. If lactic acidosis occurs, the benefits of continued use of linezolid should be weighed against the potential risks. Doctor should be informed before the treatment of any

Risk	What is known	Preventability
		previous history of lactic acidosis and all other concomitant medications.
Nerve disorders affecting vision or hands and feet (Peripheral and optic neuropathy)	Nerve disorders (Peripheral neuropathy, as well as optic neuropathy and optic neuritis) sometimes progressing to loss of vision, 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 nerve disorders when linezolid is used in patients currently taking or who have recently taken medications for the treatment of tuberculosis.	All patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary. If patients are taking Linezolid Orion for longer than the recommended 28 days, their visual function should be regularly monitored. If nerve disorders occur, the continued use of Linezolid Orion should be weighed against the potential risks. Doctor should be informed before the treatment of any previous history of nerve disorders and all other concomitant medications.
Symptoms caused by excessive accumulation of serotonin in body (Serotonin syndrome)	Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and certain medications (serotonergic agents i.e. medicines that increase the amount of serotonin) including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and medicines for migraine called triptans, have been reported. Co-administration of linezolid and serotonergic agents is therefore contraindicated except where administration of linezolid and concomitant serotonergic agents is essential. In those cases patients should be closely observed for signs and symptoms of serotonin syndrome.	Doctor should be informed of all concomitant medications before the treatment so that risky combinations can be avoided. If signs or symptoms of serotonin syndrome, such as "brain fog" (cognitive dysfunction), fever, overactive or overresponsive reflexes and coordination disturbances occur, doctor should be contacted immediately.
Seizures/epileptic fits (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	Doctor should be informed before the treatment of any previous history of seizures and all other concomitant medications.
Damaged or significantly reduced number of mitochondria ("power plants") of body's cells (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	Careful monitoring of the patient so that possible adverse effects can be detected as early as possible.

Risk	What is known	Preventability
	the drug is used longer than 28 days.	
Antibiotic-associated inflammation of the colon (Pseudomembranous colitis)	Antibiotic-associated diarrhoea and antibiotic-associated colitis, including pseudomembranous colitis and Clostridium difficile-associated diarrhoea, has been reported in association with the use of nearly all antibiotics including linezolid and may range in severity from mild diarrhoea to fatal colitis. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of linezolid	Doctor should be informed if diarrhoea appears during treatment or soon after. If antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents, including linezolid, should be discontinued and adequate therapeutic measures should be initiated immediately. Drugs against diarrhoea inhibiting bowel movements (such as loperamide) should not be used in this situation.
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	Doctor should carefully weigh benefits and risks for treatment period longer than 28 days. If prolonged treatment is necessary patient's condition should be closely monitored.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Increased risk of death in patients with infections related to catheters (Increased risk of fatal outcome in subsets of patients with , especially those with Gram negative organisms)	Excess mortality was seen in patients treated with linezolid, relative to certain other antibiotics (vancomycin/dicloxacillin/oxacillin), in an open-label study in seriously ill patients with intravascular catheter-related infections. 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 (certain types of bacteria) if there are no alternative treatment options available. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

Missing information

Risk	What is known
Fertility, pregnancy and lactation	Linezolid reversibly decreased fertility and induced abnormal sperm morphology in adult male rats at exposure levels approximately equal to those expected in humans; possible effects of linezolid on the human male reproductive system are not known. There are no adequate data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity. A potential risk for humans exists. Linezolid should not be used during pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the theoretical risk. Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration.

Risk	What is known
Use in patients with insufficient kidney function (Use in severe renal insufficiency)	In 24 patients with severely insufficient kidney function, 21 of whom were on regular haemodialysis, peak plasma concentrations of the two major metabolites after several days dosing were about 10-fold those seen in patients with normal kidney function. Peak plasma levels of linezolid were not affected. The clinical significance of these observations has not been established as limited safety data are currently available. Linezolid should be used with special caution in patients with severe kidney insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk.
Use in patients with insufficient liver function (Use in hepatic insufficiency)	The absorption, distribution, metabolism and excretion of linezolid in patients with severe hepatic insufficiency has not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism. It is recommended that linezolid should be given to patients with severe liver insufficiency only when the perceived benefit outweighs 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. The Summary of Product Characteristics and the Package leaflet for this medicinal product can be found in the national authority's web page.

This medicine has no additional risk minimisation measures.

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.