PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

VI.1. Elements for summary tables in the EPAR

VI.1.1. Summary of Safety concerns

Summary of safety concerns	
Important identified risks	- Myelosuppression - Lactic acidosis - Peripheral neuropathy - Optic neuropathy - Serotonin syndrome - Convulsions - Mitochondrial toxicity
Important potential risks	- Increased risk of fatal outcome in subset of patients with CRI, especially those with Gram negative organisms - Cardiac effects
Missing information	- Long-term use - Pregnant and lactating women

VI.1.2. Table of on-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Not applicable.

VI.1.3. Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4. Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk		
Myelosuppression	In SmPC: Warning in section 4.4 Listed in section 4.8	None proposed
Lactic acidosis	In SmPC: Warning in section 4.4 Listed in section 4.8	None proposed
Peripheral neuropathy	In SmPC: Warning in section 4.4 Listed in section 4.8	None proposed
Optic neuropathy	In SmPC: Warning in section 4.4 Listed in section 4.8	None proposed
Serotonin syndrome	In SmPC: Contraindications in section 4.3 Warning in section 4.4 Interaction in section 4.5 Listed in section 4.8	None proposed
Convulsions	In SmPC: Warning in section 4.4 Listed in section 4.8	None proposed
Mitochondrial toxicity	In SmPC: Warning in section 4.4	None proposed
Important potential risks		
Increased risk of fatal outcome in subset of patients with CRI, especially those with Gram negative organisms	In SmPC: Warning in section 4.4	None proposed
Cardiac effects	In SmPC: Listed in section 4.8	None proposed
Missing information		
Long-term use	In SmPC: Warning in section 4.4	None proposed
Pregnant and lactating women	In SmPC: Contraindications in section 4.3 Fertility, pregnancy and lactation in 4.6 Preclinical safety data in 5.3	None proposed

VI.2. Elements for a public summary

VI.2.1. Overview of disease epidemiology

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 is indicated for the treatment of **community acquired pneumonia** and **nosocomial pneumonia** when known or suspected to be caused by susceptible Gram positive bacteria. In determining whether linezolid is an appropriate treatment, the results of microbiological tests or information on the prevalence of resistance to antibacterial agents among Gram positive bacteria should be taken into consideration.

Linezolid is not active against infections caused by Gram negative pathogens. Specific therapy against Gram negative organisms must be initiated concomitantly if a Gram negative pathogen is documented or suspected.

Linezolid is indicated for the treatment of **complicated skin and soft tissue infections** only when microbiological testing has established that the infection is known to be caused by susceptible Gram positive bacteria.

Linezolid is not active against infections caused by Gram negative pathogens. Linezolid should only be used in patients with complicated skin and soft tissue infections 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 concomitantly.

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

The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Community-acquired pneumonia (CAP) is one of the most common infectious diseases and is an important cause of mortality and morbidity worldwide. It causes problems like difficulty in breathing, fever, chest pains, and a cough. CAP occurs because the areas of the lung which absorb oxygen (alveoli) from the atmosphere become filled with fluid and cannot work effectively.

Nosocomial pneumonia is defined as pneumonia that occurs more than 48 hours after hospital admission but that was not incubating at the time of admission.

Skin and soft tissue infections (SSTIs) are common, and complicated SSTIs (cSSTIs) are the more extreme end of this clinical spectrum, encompassing a range of clinical presentations such as deep-seated infection, a requirement for surgical intervention, the presence of systemic signs of sepsis, the presence of complicating co-morbidities, accompanying neutropenia, accompanying ischaemia, tissue necrosis, burns and bites. *Staphylococcus aureus* is the commonest cause of SSTI across all continents.

VI.2.2. Summary of treatments benefits

Linezolid Combino Pharm solution for infusion is the generic version of the reference product *Zyvoxid® solution for infusion*, authorised in EU and USA since years ago.

The safety and efficacy of products containing this active substance are demonstrated by his continued clinical use.

Several studies with linezolid have been published: in the FDA Website, in the Summary of Product Characteristics (SmPC) authorised in EU and also in different bibliographical references. These studies demonstrated the efficacy and safety of this product.

Some of the studies described the efficacy of linezolid in the indications approved (in one study, adult patients with clinically and radiologically documented nosocomial pneumonia were enrolled in a randomized, multi-center, double-blind trial. In another study, adult patients with clinically documented complicated skin and skin structure infections were enrolled in a randomized, multi-center, double-blind, double-dummy trial comparing study medications administered intravenously followed by medications given orally for a total of 10 to 21 days of treatment) and some others described for example, possible interactions (the potential drug-drug interaction with dextromethorphan was studied in healthy volunteers), safety information or use in paediatric population (the efficacy of linezolid (10 mg/kg q8h) administered intravenously was compared to vancomycin (10-15mg/kg q6-24h) in treating infections due to suspected or proven resistant gram-positive pathogens(including nosocomial pneumonia, complicated skin and skin structure infections, catheter related bacteraemia, bacteraemia of unknown source, and other infections), in children from birth to 11 years. Clinical cure rates in the clinically evaluable population were 89.3% (134/150) and 84.5% (60/71) for linezolid and vancomycin, respectively (95%CI: -4.9, 14.6)).

VI.2.3. Unknowns relating to treatments benefits

According to the authorised Summary of Product Characteristics, the following unknowns relating to treatment benefits are described:

- The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.
- The safety and efficacy of linezolid in children and adolescents (< 18 years old) have not been established.

VI.2.4. Summary of safety concerns

Important identified risks

Risk	What is know	Preventability
Myelosuppression	**Warning in section 4.4** Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pretreatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with linezolid may be at greater risk of experiencing blood dyscrasias than younger patients. Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis. Therefore, close monitoring of blood counts is recommended in patients who: have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 10-14 days of therapy. Linezolid should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible. If significant myelosuppression occurs during	In SmPC: Warning in section 4.4 Listed in section 4.8

	linezolid therapy, treatment should be stopped unless it is considered absolutely necessary to continue therapy, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented. In addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count. In compassionate use studies, a higher incidence of serious anaemia was reported in patients receiving linezolid for more than the maximum recommended duration of 28 days. These patients more often required blood transfusion. Cases of anaemia requiring blood transfusion have also been reported post marketing, with more cases occurring in patients who received linezolid therapy for more than 28 days. Cases of sideroblastic anaemia have been reported post-marketing. Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered following discontinuation of linezolid with or without treatment for their anaemia. **Listed in section 4.8** *Blood and the lymphatic system disorders* Frequency not known (cannot be estimated from available data): Myelosuppression	
Lactic acidosis	**Warning in section 4.4** Lactic acidosis has been reported with the use of linezolid. Patients who develop signs and symptoms of metabolic acidosis including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level, 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. **Listed in section 4.8** *Metabolism and nutrition disorders* Frequency not known (cannot be estimated from available data): Lactic acidosis	In SmPC: Warning in section 4.4 Listed in section 4.8
Peripheral neuropathy	**Warning in section 4.4**	In SmPC:

	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. If peripheral neuropathy occurs, the continued use of Linezolid should be weighed against the potential risks. There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis. **Listed in section 4.8** *Nervous system disorders* Frequency not known (cannot be estimated from available data): Peripheral neuropathy	Warning in section 4.4 Listed in section 4.8
Optic neuropathy	**Warning in section 4.4** 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. 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 any patients are taking Linezolid for longer than the recommended 28 days, their visual function should be regularly monitored. If optic neuropathy occurs, the continued use of Linezolid should be weighed against the potential risks. There may be an increased risk of neuropathies when linezolid is used in patients currently taking or who have recently taken antimycobacterial medications for the treatment of tuberculosis. **Listed in section 4.8** *Eye disorders* Frequency not known (cannot be estimated from available data): Optic neuropathy	In SmPC: Warning in section 4.4 Listed in section 4.8

Serotonin syndrome	**Contraindications in section 4.3** Patients taking any of the following medications: serotonin re-uptake inhibitors, serotonin 5-HT1 receptor agonists (triptans). **Warning in section 4.4.** *Serotonin syndrome* Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) 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 such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur physicians should consider discontinuing either one or both agents; if the concomitant serotonergic agent is withdrawn, discontinuation symptoms can occur. **Interactions in section 4.5** *Potential serotonergic interactions* The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20 mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan. Post marketing experience: there has been one report of a patient experiencing serotonin syndrome-like effects while taking linezolid and dextromethorphan which resolved on discontinuation of both medications. During clinical use of linezolid with serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), cases of serotonin syndrome have been reported. Therefore, while co-administration is contraindicated, management of patients for whom treatment with linezolid and serotonergic agents is essential.	In SmPC: Contraindications in section 4.3 Warning in section 4.4 Medical interaction in section 4.5 Listed in section 4.8

	Listed in section 4.8 *Nervous system disorders* Frequency not known (cannot be estimated from available data): Serotonin syndrome	
Convulsions	**Warning in section 4.4** 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. Patients should be advised to inform their physician if they have a history of seizures. **Listed in section 4.8** *Nervous system disorders* Frequency not known (cannot be estimated from available data): Convulsions	In SmPC: Warning in section 4.4 Listed in section 4.8
Mitochondrial toxicity	**Warning in section 4.4** 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.	In SmPC: Warning in section 4.4
Increased risk of fatal outcome in subset of patients with CRI, especially those with Gram negative organisms	**Warning in section 4.4** *Mortality imbalance in a clinical trial in patients with catheter-related Gram positive bloodstream infections* Excess mortality was seen in patients treated with linezolid, relative to vancomycin/dicloxacillin/oxacillin, in an open-label study in seriously ill patients with intravascular catheter-related infections [78/363 (21.5%) vs 58/363 (16.0%)]. The main factor influencing the mortality rate was the Gram positive infection status at baseline. Mortality rates were similar in patients with infections caused purely by Gram positive organisms (odds ratio 0.96; 95% confidence interval: 0.58-1.59) but were significantly higher (p=0.0162) in the linezolid arm in patients with any other pathogen or no pathogen at baseline (odds ratio 2.48; 95% confidence interval: 1.38-4.46). The greatest imbalance occurred during treatment and within 7 days following discontinuation of study drug. More patients in the linezolid arm acquired Gram negative pathogens during the study and died from infection caused by Gram negative	In SmPC: Warning in section 4.4

	pathogens and polymicrobial 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 if there are no alternative treatment options available. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.	
Cardiac effects	**Listed in section 4.8** Cardiac disorders Rare: Arrhythmia (tachycardia)	In SmPC: Listed in section 4.8
Long-term use	**Warning in section 4.4** *Clinical trials* The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.	In SmPC: Warning in section 4.4
Pregnant and lactating women	**Contraindications in section 4.3** Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration. **Fertility, pregnancy and lactation in section 4.6** 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. **Preclinical safety data in section 5.3** Linezolid and its metabolites are excreted into the milk of lactating rats and the concentrations observed were higher than those in maternal plasma.	In SmPC: Contraindications in section 4.3 Fertility, pregnancy and lactation in 4.6 Preclinical safety data in 5.3

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

Not applicable.

VI.2.6. Planned post authorisation development plan

Not applicable.

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

Not applicable.