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5th March 2007

Dear Healthcare Professional,

IMPORTANT SAFETY INFORMATION

Zyvox™ (linezolid injection, tablets, and oral suspension): results from a clinical study of catheter-related Gram-positive bloodstream infections leading to a restriction of indication in complicated skin and soft tissue infections.

- **Linezolid should be used in the treatment of complicated skin and soft-tissue infections only when microbiological testing shows that the infection is caused by susceptible Gram positive bacteria.**
- **Patients with complicated skin and soft-tissue infections that are known or suspected to be caused by co-infection with Gram positive and Gram negative pathogens should only be treated with linezolid when no other treatment options are available. In these situations treatment against Gram negative pathogens must be initiated concomitantly.**

We are writing to inform you about an update to the prescribing advice for linezolid following an open-label study of seriously ill patients with intravascular catheter-related infections. This study showed an increased number of deaths up to 84 days after first dose of study drug in patients treated with linezolid (78 of 363 [21·5%]) compared with those treated with vancomycin, dicloxacillin, or oxacillin (58 of 363 [16·0%]). The greatest imbalance occurred during treatment and within 7 days following discontinuation of study drug with 43/363 (12%) deaths in the linezolid arm vs. 22/363 (6%) in the comparator arm. From 8 days post-treatment, mortality rates in both study arms were similar (35 vs. 36 patients). Mortality did not differ between groups for patients with infections caused purely by Gram positive organisms, but was significantly higher in the linezolid group for patients infected with any other pathogen or with no pathogen at baseline. More patients in the linezolid group acquired Gram negative pathogens during the study and died from infections caused by Gram negative pathogens or polymicrobial infections. Even if patients with Gram negative pathogens received 'adequate' antibiotic therapy, death rates were still higher in the linezolid arm.

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Prescribing advice

Linezolid is not active against Gram negative infections.

Complicated skin and soft-tissue infections

Linezolid should be used to treat complicated skin and soft-tissue infections **only** when microbiological testing shows that infection is caused by susceptible Gram positive bacteria. Furthermore, linezolid should be used to treat patients with complicated skin and soft-tissue infections that are known or suspected to be caused by co-infection with Gram positive and Gram negative pathogens **only** if there are no other treatment options available. In these circumstances, treatment against Gram negative pathogens must be initiated concomitantly.

Nosocomial pneumonia and community-acquired pneumonia

Linezolid can be used for the treatment of community-acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram positive bacteria. Specific therapy against Gram negative pathogens must be started at the same time if a Gram negative pathogen is documented or suspected.

The revised Product Information (see Annex) has been approved by the EMEA CHMP Pharmacovigilance Working Party (PhVWP) and the Irish Medicines Board (IMB).

Further information

This study was an open-label, randomised, phase III clinical trial that enrolled 726 patients aged 13 years or older for catheter-related Gram positive bloodstream infections that were regarded as a subset of complicated skin and soft-tissue infections. Overall 39% of the patients enrolled in this study had positive blood cultures, a much higher rate than that observed in studies of complicated skin and soft tissue infections. About 50% of patients were being treated in an intensive care unit and 25% were being mechanically ventilated. Patients were randomly assigned to 600 mg linezolid given intravenously or orally every 12 h, or to 1 g vancomycin given intravenously every 12 h; those in the vancomycin group who were subsequently identified as having methicillin-susceptible Gram positive infection were switched to oxacillin (2 g intravenously every 6 h), and those who were subsequently identified as having methicillin-susceptible coagulase-negative staphylococci infection could later be switched to dicloxacillin (500 mg orally every 6 h). Treatment duration was 7–28 days.

The main factor that affected mortality was Gram positive infection status at baseline. Mortality rates did not differ between groups for patients with pure Gram positive infections, including *Staphylococcus aureus* (odds ratio 0·96 [95% CI 0·58–1·59]), but were significantly higher in the linezolid group than in the comparator group for patients with any other pathogen or no pathogen at baseline (2·48 [1·38–4·46], p=0·0162). More patients in the linezolid group acquired infections caused by Gram negative pathogens during the study and died from infections caused by Gram negative pathogens or polymicrobial infections. Even if patients with Gram negative pathogens received 'adequate' antibiotic therapy, death rates were still higher in the linezolid arm. Potential mechanisms that might explain the findings of this trial are under investigation.

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Changes to the Summary of Product Characteristics (SPC)

Sections 4.1 (Therapeutic Indications), 4.4 (Special Warnings and Special Precautions for Use) and 5.1 (Pharmacodynamic Properties) of the SPC for Zyvox™ have been amended. The complete SPC with amendments highlighted is appended to this letter.

Reporting of suspected adverse events

Please report any suspected adverse reactions in association with use of Zyvox™ to Pfizer Medical Information Department at Pfizer Limited, Walton Oaks, Dorking Road, Walton-on-the-Hill, Surrey, KT20 7NS, United Kingdom or to the Irish Medicines Board in the usual way. Pfizer Limited UK can be contacted on freephone 1800 633 363. Please ask for the Drug Safety Group.

Communication information

If you have any enquiries or need additional information, please contact Pfizer Medical Information Department at Pfizer Limited, Walton Oaks, Dorking Road, Walton-on-the-Hill, Surrey, KT20 7NS, United Kingdom. The following freephone number is available for provision of medical information during normal working hours and for out of hours medical emergencies: 1800 633 363. Please ask for the Medical Information group.

Yours sincerely,

Dr. John Farrell
Medical Director

Annex
Summary of Product Characteristics (February 2007)

1. NAME OF THE MEDICINAL PRODUCT

Zyvox 2 mg/ml Solution for Infusion
Zyvox 600 mg Film-Coated Tablets
Zyvox 100 mg/5 ml Granules for Oral Suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for Infusion
1 ml contains 2 mg linezolid. 300 ml infusion bags contain 600 mg linezolid.

Tablets
Each tablet contains 600 mg linezolid.

Granules for Oral Suspension
Following reconstitution with 123 ml water, each 5 ml contains 100 mg linezolid.

For excipients, see section 6.1

3. PHARMACEUTICAL FORM

Solution for infusion.
Isotonic, clear, colourless to yellow solution.

Film-coated tablet
White, ovaloid tablet with "ZYVOX 600 mg" printed on one side.

Granules for oral suspension
White to light-yellow, orange flavoured granules

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Nosocomial pneumonia
Community acquired pneumonia

Zyvox 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 Zyvox 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. (See section 5.1 for the appropriate organisms).

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.

Complicated skin and soft tissue infections (see Section 4.4)

Zyvox 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 (see section 4.4). 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.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and Method of Administration

Zyvox solution for infusion, film-coated tablets or oral suspension may be used as initial therapy.

Patients who commence treatment on the parenteral formulation may be switched to either oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as linezolid has an oral bioavailability of approximately 100%.

Recommended dosage and duration of treatment for adults:
The duration of treatment is dependent on the pathogen, the site of infection and its severity, and on the patient's clinical response.
The following recommendations for duration of therapy reflect those used in the clinical trials.

Shorter treatment regimens may be suitable for some types of infection but have not been evaluated in clinical trials.

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. (see section 4.4).

No increase in the recommended dosage or duration of treatment is required for infections associated with concurrent bacteraemia.

The dose recommendation for the solution for infusion and the tablets/granules for oral suspension are identical and are as follows:

Infections	Dosage	Duration of treatment
Nosocomial pneumonia	600 mg twice daily	10-14 Consecutive days
Community acquired pneumonia		
Complicated skin and soft tissue infections	600 mg twice daily	

Children: There are insufficient data on the, safety and efficacy of linezolid in children and adolescents (< 18 years old) to establish dosage recommendations (see section 5.2).

Therefore, until further data are available, use of linezolid in this age group is not recommended.

Elderly patients: No dose adjustment is required.

Patients with renal insufficiency: No dose adjustment is required (see sections 4.4 and 5.2).

Patients with severe renal insufficiency (i.e. CLCR < 30 ml/min): No dose adjustment is required. Due to the unknown clinical significance of higher exposure (up to 10-fold) to the two primary metabolites of linezolid in patients with severe renal insufficiency, linezolid should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

As approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by haemodialysis, but the concentrations of these metabo lites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore, 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.

To date, there is no experience of linezolid administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than haemodialysis).

Patients with hepatic insufficiency: No dose adjustment is required. However, 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 (see sections 4.4 and 5.2).

Method of Administration

The recommended linezolid dosage should be administered intravenously or orally twice daily.

Solution for infusion

Route of administration: Intravenous use.

The solution for infusion should be administered over a period of 30 to 120 minutes.

Tablets/Granules for Oral Suspension

Route of administration: Oral use

The film-coated tablets may be taken with or without food.

The oral suspension may be taken with or without food.

Granules for Oral Suspension

A 600 mg dose is provided by 30 ml of reconstituted suspension (i.e. six 5 ml spoonfuls).

4.3 Contraindications

Patients hypersensitive to linezolid or any of the excipients (see section 6.1).

Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid, selegiline, moclobemide) or within two weeks of taking any such medicinal product.

Unless there are facilities available for close observation and monitoring of blood pressure, linezolid should not be administered to patients with the following underlying clinical conditions or on the following types of concomitant medications:

- Patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states.
- Patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), directly and indirectly acting sympathomimetic agents (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), dopaminergic agents (e.g. dopamine, dobutamine), pethidine or buspirone.

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration (see section 4.6).

4.4 Special Warnings and Special Precautions for Use

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI); however, at the doses used for antibacterial therapy, it does not exert an anti-depressive effect. There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients with underlying conditions and/or on concomitant medications which might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see sections 4.3 and 4.5).

Patients should be advised against consuming large amounts of tyramine rich foods (see section 4.5).

Solution for infusion

Each ml of the solution contains 45.7 mg (i.e. 13.7 g/300 ml) glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance. Each ml of solution also contains 0.38 mg (114 mg/300 ml) sodium.

Granules for oral suspension

The reconstituted oral suspension contains a source of phenylalanine (aspartame) equivalent to 20 mg/5 ml. Therefore, this formulation may be harmful for people with phenylketonuria. For patients with phenylketonuria, Zyvox solution for infusion or tablets are recommended.

The suspension also contains sucrose, mannitol and sodium equivalent to 1.7 mg/ml. Therefore, it should not be administered to patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency. Due to its mannitol content, the oral suspension may have a mild laxative effect. The product contains 8.5 mg sodium per 5 ml dose. The sodium content should be taken into account in patients on a controlled sodium diet.

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. 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 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.

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.

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 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 (see section 4.1). In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

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.

Linezolid should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk (see sections 4.2 and 5.2).

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk (see sections 4.2 and 5.2).

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent. In cases of suspected or verified antibiotic–associated colitis, discontinuation of linezolid may be warranted. Appropriate management measures should be instituted.

The effects of linezolid therapy on normal flora have not been evaluated in clinical trials.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. For example, approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. Should superinfection occur during therapy, appropriate measures should be taken.

The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.

Peripheral neuropathy and optic neuropathy, sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX; 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 Zyvox for longer than the recommended 28 days, their visual function should be regularl monitored.

If peripheral or optic neuropathy occurs, the continued use of Zyvox in these patients should be weighed against the potential risks.

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 (see section 5.3).

4.5 Interaction with Other Medicaments and Other Forms of Interaction

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). There are very limited data from drug interaction studies and on the safety of linezolid when administered to patients on concomitant medications that might put them at risk from MAO inhibition. Therefore, linezolid is not recommended for use in these circumstances unless close observation and monitoring of the recipient is possible (see section 4.3).

In normotensive healthy volunteers, linezolid enhanced the increases in blood pressure caused by pseudoephedrine and phenylpropanolamine hydrochloride. Co-administration of linezolid with either pseudoephedrine or phenylpropanolamine resulted in mean increases in systolic blood pressure of the order of 30-40 mm Hg, compared with 11-15 mm Hg increases with linezolid alone, 14-18 mm Hg with either pseudoephedrine or phenylpropanolamine alone and 8-11 mm Hg with placebo. Similar studies in hypertensive subjects have not been conducted. It is recommended that doses of drugs with a vasopressive action, including dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered with linezolid.

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 serotonin re-uptake inhibitors, cases of serotonin syndrome have been very rarely reported (see sections 4.3 and 4.8).

No significant pressor response was observed in subjects receiving both linezolid and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting excessive amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced drug interactions are expected with linezolid.

When warfarin was added to linezolid therapy at steady-state, there was a 10% reduction in mean maximum INR on co-administration with a 5% reduction in AUC INR. There are insufficient data from patients who have received warfarin and linezolid to assess the clinical significance, if any, of these findings.

4.6 Pregnancy and Lactation

There are no adequate data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). 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.

4.7 Effects on Ability to Drive and Use Machines

Patients should be warned about the potential for dizziness whilst receiving linezolid and should be advised not to drive or operate machinery if dizziness occurs.

4.8 Undesirable Effects

The information provided is based on data generated from clinical studies in which more than 2,000 adult patients received the recommended linezolid doses for up to 28 days.

Approximately 22% of patients experienced adverse reactions; those most commonly reported were headache (2.1%), diarrhoea (4.2%), nausea (3.3%) and candidiasis (particularly oral [0.8%] and vaginal [1.1%] candidiasis, see table below).

The most commonly reported drug-related adverse events which led to discontinuation of treatment were headache, diarrhoea, nausea and vomiting. About 3% of patients discontinued

treatment because they experienced a drug-related adverse event.

Adverse drug reactions occurring at frequencies ≥ 0.1%
General body
Common: Headache; candidiasis (particularly oral and vaginal candidiasis) or fungal infection.
Uncommon: Localised or general abdominal pain; chills; fatigue; fever; injection site pain; phlebitis / thrombophlebitis; localised pain.
Blood and the lymphatic system disorders
Uncommon: (Frequency as reported by clinician): Eosinophilia, leucopenia, neutropenia, thrombocytopenia.
Metabolism and nutrition disorders
Common: Abnormal liver function tests.
Nervous system disorders
Uncommon: Dizziness, hypoaesthesia, insomnia, paraesthesia.
Special senses
Common: Taste perversion (metallic taste).
Uncommon: Blurred vision, tinnitus.
Cardiovascular disorders
Uncommon: Hypertension.
Gastrointestinal disorders
Common: Diarrhoea, nausea, vomiting.
Uncommon: Constipation; dry mouth; dyspepsia; gastritis; glossitis; increased thirst; loose stools; pancreatitis; stomatitis; tongue discolouration or disorder.
Skin disorders
Uncommon: Dermatitis, diaphoresis, pruritus, rash, urticaria.
Urogenital disorders
Uncommon: Vulvovaginal disorder, polyuria, vaginitis.
Laboratory abnormalities (according to definitions applied during clinical trials) occurring at frequencies ≥ 0.1%
Chemistry
Common: Increased AST, ALT, LDH, alkaline phosphatase, BUN, creatine kinase, lipase, amylase or non fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate.
Uncommon: Increased total bilirubin, creatinine, sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride.
Haematology
Common: Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.
Uncommon: Increased reticulocyte count. Decreased neutrophils.
Common ≥1/100 and <1/10 or ≥ 1% and < 10% — Uncommon ≥ 1/1,000 and < 1/100 or ≥ 0.1% and <1%

The following adverse reactions to linezolid were considered to be serious in isolated cases: localised abdominal pain, transient ischaemic attacks, hypertension, pancreatitis & renal failure.

During clinical trials, a single case of arrhythmia (tachycardia) was reported as drug related. Seizures were reported in 10 patients of which none was considered to be drug related.
In controlled clinical trials where linezolid was administered for up to 28 days, less than 0.1% of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for >28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for >28 days.

Post marketing experience:
Haematology: Anaemia, leucopenia, neutropenia, thrombocytopenia, pancytopenia and myelo suppression (see section 4.4). Of the cases reporting anaemia, more patients required blood transfusion when treated with linezolid for longer than the maximum recommended duration of 28 days (see section 4.4).

Lactic acidosis has been reported with the use of Zyvox (see section 4.4).

Neuropathies: Peripheral neuropathy and/or optic neuropathy, sometimes progressing to loss of vision, have been reported in patients treated with ZYVOX; these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days.
Skin: Very rare reports of bullous skin disorders such as those described as Stevens-Johnson syndrome have been received.

Cases of serotonin syndrome have been very rarely reported (see sections 4.3 and 4.5)

4.9 Overdosage

No specific antidote is known.

No cases of overdose have been reported. However, the following information may prove useful:

Supportive care is advised together with maintenance of glomerular filtration. Approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

Signs of toxicity in rats following doses of 3000 mg/kg/day linezolid were decreased activity and ataxia whilst dogs treated with 2000 mg/kg/day experienced vomiting and tremors.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Other antibacterials.
ATC code: J01X X08

General Properties

Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, the oxa zolidinones. 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.

Specifically, it binds to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

The in-vitro postantibiotic effect (PAE) of linezolid for Staphylococcus aureus was approximately 2 hours. When measured in animal models, the in-vivo PAE was 3.6 and 3.9 hours for Staphylococcus aureus and Streptococcus pneumoniae, respectively. In animal studies, the key pharmacodynamic parameter for efficacy was the time for which the linezolid plasma level exceeded the minimum inhibitory concentration (MIC) for the infecting organism.

Breakpoints

- The general MIC breakpoint to identify organisms susceptible to linezolid is ≤ 2 mg/l.
- There are limited data to suggest that staphylococcal and enterococcal species for which the MIC linezolid is 4 mg/l may be successfully treated.
- All organisms for which the MIC of linezolid is ≥ 8 mg/l (i.e. > 4 mg/l) linezolid should be considered resistant.

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Only micro - organisms relevant to the given clinical indications are presented here.

Category
Susceptible organisms
Gram positive aerobes:
Enterococcus faecalis
*Enterococcus faecium**
*Staphylococcus aureus**
Coagulase negative staphylococci

*Streptococcus agalactiae**
*Streptococcus pneumoniae**
*Streptococcus pyogenes**
Group C streptococci
Group G streptococci
Gram positive anaerobes:
Clostridium perfringens
Peptostreptococcus anaerobius
Peptostreptococcus species
Resistant organisms
Haemophilus influenzae
Moraxella catarrhalis
Neisseria species
Enterobacteriaceae
Pseudomonas species

*Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Whereas linezolid shows some in vitro activity against *Legionella, Chlamydia pneumoniae* and *Mycoplasma pneumoniae*, there are insufficient data to demonstrate clinical efficacy.

Resistance

Cross resistance

Linezolid's mechanism of action differs from those of other antibiotic classes. In vitro studies with clinical isolates (including methicillin-resistant staphylococci, vancomycin-resistant enterococci, and penicillin - and erythromycin-resistant streptococci) indicate that linezolid is usually active against organisms which are resistant to one or more other classes of antimicrobial agents.

Resistant mutant frequency

Resistant mutant frequency to linezolid occurs in vitro at a frequency of 1×10^{-9} to 1×10^{-11} and is associated with point mutations in the 23S rRNA. Linezolid-resistant organisms were recovered from six patients infected with *E. faecium* (four patients received 200 mg Q12h and two patients received 600 mg Q12h) in clinical trials and in eight patients with *E. faecium* and in one patient with *E. faecalis* treated in the expanded access programme. All patients had prosthetic devices that were not removed or abscesses that were not drained.

5.2 Pharmacokinetic Properties

Zyvox primarily contains (s)-linezolid which is biologically active and is metabolised to form inactive derivatives.

Absorption

Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing.

Absolute oral bioavailability of linezolid (oral and intravenous dosing in a crossover study) is complete (approximately 100%).

Absorption is not significantly affected by food and absorption from the oral suspension is similar to that achieved with the film-coated tablets.

Plasma linezolid C_{max} and C_{min} (mean and [SD]) at steady-state following twice daily intravenous dosing of 600 mg have been determined to be 15.1 [2.5] mg/l and 3.68 [2.68] mg/l, respectively.

In another study following oral dosing of 600 mg twice daily to steady-state, C_{max} and C_{min} were determined to be 21.2 [5.8] mg/l and 6.15 [2.94] mg/l, respectively. Steady-state conditions are achieved by the second day of dosing.

Distribution

Volume of distribution at steady-state averages at about 40-50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31% and is not concentration dependent.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in volunteer studies following multiple dosing. The ratio of linezolid in saliva and sweat relative to plasma was 1.2:1.0 and 0.55:1.0, respectively. The ratio for epithelial lining fluid and alveolar cells of the lung was 4.5:1.0 and 0.15:1.0, when measured at steady-state C_{max}, respectively.

In a small study of subjects with ventricular-peritoneal shunts and essentially non-inflamed meninges, the ratio of linezolid in cerebrospinal fluid to plasma at C_{max} was 0.7:1.0 after multiple linezolid dosing.

Metabolism

Linezolid is primarily metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives; the aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite (PNU-142586). The hydroxyethyl glycine metabolite (PNU-142586) is the predominant human metabolite and is believed to be formed by a non-enzymatic process. The aminoethoxyacetic acid metabolite (PNU-142300) is less abundant. Other minor, inactive metabolites have been characterised.

Elimination

In patients with normal renal function or mild to moderate renal insufficiency, linezolid is primarily excreted under steady-state conditions in the urine as PNU-142586 (40%), parent drug (30%) and PNU-142300 (10%). Virtually no parent drug is found in the faeces whilst approximately 6% and 3% of each dose appears as PNU-142586 and PNU-142300, respectively. The elimination half-life of linezolid averages at about 5-7 hours.

Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. A small degree of non-linearity in clearance is observed with increasing doses of linezolid. This appears to be due to lower renal and non-renal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.

Special Populations

Patients with renal insufficiency: After single doses of 600 mg, there was a 7-8-fold increase in exposure to the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e. creatinine clearance < 30 ml/min). However, there was no increase in AUC of parent drug. Although there is some removal of the major metabolites of linezolid by haemodialysis, metabolite plasma levels after single 600 mg doses were still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

In 24 patients with severe renal insufficiency, 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 renal 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 (see sections 4.2 and 4.4).

Patients with hepatic insufficiency: Limited data indicate that the pharmacokinetics of linezolid, PNU-142300 and PNU-142586 are not altered in patients with mild to moderate hepatic insufficiency (i.e. Child-Pugh class A or B). The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e. Child-Pugh class C) have 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 (see sections 4.2 and 4.4).

Children and adolescents (< 18 years old): There are insufficient data on the safety and efficacy of linezolid in children and adolescents (< 18 years old) and therefore, use of linezolid in this age group is not recommended.(see section 4.2). Further studies are needed to establish safe and effective dosage recommendations. Pharmacokinetic studies indicate that after single and multiple doses in children (1 week to 12 years), linezolid clearance (based on kg body weight) was greater in paediatric patients than in adults, but decreased with increasing age.
In children 1 week to 12 years old, administration of 10 mg/kg every 8 hours daily gave exposure approximating to that achieved with 600 mg twice daily in adults. In neonates up to 1 week of age, the systemic clearance of linezolid (based on kg body weight) increases rapidly in the first week of life. Therefore, neonates given 10 mg/kg every 8 hours daily will have the greatest systemic exposure on the first day after delivery. However, excessive accumulation is not expected with this dosage regimen during the first week of life as clearance increases rapidly over that period.
In adolescents (12 to 17 years old), linezolid pharmacokinetics were similar to that in adults following a 600mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that observed in adults receiving the same dosage.

Elderly patients: The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 and over.

Female patients: Females have a slightly lower volume of distribution than males and the mean clearance is reduced by approximately 20% when corrected for body weight. Plasma concentrations are higher in females and this can partly be attributed to body weight differences. However, because the mean half life of linezolid is not significantly different in males and females, plasma concentrations in females are not expected to substantially rise above those known to be well tolerated and, therefore, dose adjustments are not required.

5.3 Preclinical Safety Data

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those expected in humans. In sexually mature animals these effects were reversible. However, these effects did not reverse in juvenile animals treated with linezolid for nearly the entire period of sexual maturation. Abnormal sperm morphology in testis of adult male rats and epithelial cell hypertrophy and hyperplasia in the epididymis were noted. Linezolid appeared to affect the maturation of rat spermatozoa. Supplementation of testosterone had no effect on linezolid-mediated fertility effects. Epididymal hypertrophy was not observed in dogs treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 times or equivalent, respectively, to those expected in humans.

The same linezolid concentrations caused maternal toxicity in mice and were related to increased embryo death including total litter loss, decreased fetal body weight and an exacerbation of the normal genetic predisposition to sternal variations in the strain of mice. In rats, slight maternal toxicity was noted at exposures lower than expected clinical exposures.

Mild fetal toxicity, manifested as decreased fetal body weights, reduced ossification of sternebrae, reduced pup survival and mild maturational delays were noted. When mated, these same pups showed evidence of a reversible dose-related increased in pre-implantation loss with a corresponding decrease in fertility.

Linezolid and its metabolites are excreted into the milk of lactating rats and the concentrations observed were higher than those in maternal plasma.

Linezolid produced reversible myelosupression in rats and dogs.

Preclinical data, based on conventional studies of repeated-dose toxicity and genotoxicity, revealed no special hazard for humans beyond those addressed in other sections of this Summary of Product Characteristics. Carcinogenicity / oncogenicity studies have not been conducted in view of the short duration of dosing and lack of genotoxicity in the standard battery of studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Solution for Infusion

Glucose monohydrate
Sodium citrate (E331)
Citric acid anhydrous (E330)
Hydrochloric acid (E507)
Sodium hydroxide (E524)
Water for injections

Tablets

Tablet core:
Microcrystalline cellulose (E460)
Maize starch
Sodium starch glycollate type A
Hydroxypropylcellulose (E463)
Magnesium stearate (E572)

Film coat
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400
Carnauba wax (E903)

Red ink
Red iron oxide (E172)

Granules for Oral Suspension
Sucrose
Mannitol (E421)
Microcrystalline cellulose (E460)
Carboxymethylcellulose sodium (E466)
Aspartame (E951)
Anhydrous colloidal silica (E551)
Sodium citrate (E331)
Xanthan gum (E415)
Sodium benzoate (E211)
Citric acid anhydrous (E330)
Sodium chloride
Sweetners (fructose, maltodextrin, monoammonium glycyrrhizinate, sorbitol). Orange, Orange Cream, Peppermint and Vanilla flavourings (acetoin, alpha tocopherols acetaldehyde, anisic aldehyde, beta-caryophyllene, n-butyric acid, butyl butyryl lactate, decalactone delta, dimethyl benzyl carb acetate, ethyl alcohol, ethyl butyrate, ethyl maltol, ethyl vanillin, furaneol, grapefruit terpenes, heliotropin, maltodextrin, modified food starch, monomethyl succinate, orange aldehyde, orange oil FLA CP, orange oil Valencia 2X, orange oil 5X Valencia, orange essence oil, orange juice carbonyls, orange terpenes, peppermint essential oil, propylene glycol, tangerine oil, vanilla extract, vanillin, water).

6.2 Incompatibilities

Solution for infusion

Additives should not be introduced into this solution. If linezolid is to be given concomitantly with other drugs, each drug should be given separately in accordance with its own directions for use. Similarly, if the same intravenous line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following linezolid administration with a compatible infusion solution (see section 6.6).

Zyvox solution for infusion is known to be physically incompatible with the following compounds: amphotericin B, chlorpromazine hydrochloride, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and sulphamethoxazole / trimethoprim. Additionally, it is chemically incompatible with ceftriaxone sodium.

Tablets/Granules for Oral Suspension

Not applicable

6.3 Shelf Life

Solution for Infusion

Before opening: 3 years

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Tablets

3 years

Granules for Oral Suspension

Before reconstitution: 2 years

After reconstitution: 3 weeks

6.4 Special Precautions for Storage

Solution for Infusion

Store in the original package (overwrap and carton) until ready to use.

Tablets

No special precautions for storage.

Granules for Oral Suspension

Before reconstitution: Keep the container tightly closed.

After reconstitution: Keep the container in the outer carton.

6.5 Nature and Contents of Container

Solution for Infusion

Single use, ready-to-use, latex-free, multilayered (inner layer: ethylene propylene copolymer and styrene/ethylene butylene/styrene copolymer; middle layer: styrene/ethylene butylene/styrene copolymer; outer layer: copolyester) film infusion bags sealed inside a foil laminate overwrap. The bag holds 300 ml solution and is packaged in a box. Each box contains 1*, 2**, 5, 10, 20

or 25 infusion bags.

Note:
The above boxes may also be supplied in "hospital" packs of: *5, 10 or 20. **3, 6 or 10
Not all package sizes may be marketed.

Tablets
White, HDPE bottle with a polypropylene screw cap containing either
10*, 14*, 20*, 24, 30, 50 or 60
White, HDPE bottle with a polypropylene screw cap containing 100 tablets (for hospital use only)

Note:
The above bottles may also be supplied in "hospital packs" of: *5 or 10.

Polyvinylchloride (PVC)/foil blisters of 10 tablets packaged in a box.
Each box contains either 10*, 20*, 30, 50 or 60 tablets.

Polyvinylchloride (PVC)/foil blisters of 10 tablets packaged in a box. Each box contains 100 tablets (for hospital use only).

Note:
The above boxes may also be supplied in "hospital packs" of 5 or 10.
Not all package sizes may be marketed.

Granules for Oral Suspension
Amber, Type III glass bottles with a nominal volume of 240 ml containing 66 g granules for oral suspension. Each bottle has a polypropylene, child resistant screw cap and is packaged in a box with a 2.5 ml/5 ml measuring spoon.

Note:
The above bottles may also be supplied in "hospital packs" of: 5 or 10.
Not all package sizes may be marketed.

6.6 Special precautions for disposal of used medicinal product or waste materials derived from such medicinal product and other handling of the product

Solution for Infusion
For single use only. Remove overwrap only when ready to use, then check for minute leaks by squeezing the bag firmly. If the bag leaks, do not use as sterility may be impaired. The solution should be visually inspected prior to use and only clear solutions, without particles should be used. Do not use these bags in series connections. Any unused solution must be discarded. Do not reconnect partially used bags.

Zyvox solution for infusion is compatible with the following solutions: 5% glucose intravenous infusion, 0.9% sodium chloride intravenous infusion, Ringer-lactate solution for injection (Hartmann's solution for injection).

Tablets
No special requirements.

Granules for Oral Suspension
Loosen the granules and reconstitute using 123 ml water in two approximately equal aliquots to produce 150 ml oral suspension. The suspension should be vigorously shaken between each addition of water.
Before use, gently invert the bottle a few times. Do not shake.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Ireland Limited,
9 Riverwalk, National Digital Park, City West Business Campus, Dublin 24, Ireland.

8. MARKETING AUTHORISATION NUMBER

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