PACKAGE INSERT

Front

1 cm
Barcode

hovid

hovid-Linezolid Tablet 600 mg

VILINxx-0 (EXP)

DESCRIPTION
Oblong, white film-coated tablet, bevel-edged and shallow convex faces.

COMPOSITION
Each film-coated tablet contains Linezolid 600 mg.

PHARMACODYNAMIC
General Properties
Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. It has in vitro activity against aerobic Gram positive bacteria and anaerobic micro-organisms. Linezolid selectively inhibits bacterial protein synthesis via a unique mechanism of action. 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
Minimum inhibitory concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for staphylococci and enterococci are Susceptible ≤ 4 mg/L and Resistant >4 mg/L. For streptococci (including *S. pneumoniae*) the breakpoints are Susceptible ≤2 mg/L and Resistant >4 mg/L.

Non-species related MIC breakpoints are Susceptible ≤2 mg/L and Resistant >4 mg/L. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific species. They are for use only for organisms that have not been given a specific breakpoint and not for those species where susceptibility testing is not recommended.

Susceptibility
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.

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.

Resistance to linezolid is associated with point mutations in the 23S rRNA.

As documented with other antibiotics when used in patients with difficult to treat infections and/or for prolonged periods, emergent decreases in susceptibility have been observed with linezolid. Resistance to linezolid has been reported in enterococci, Staphylococcus aureus and coagulase negative staphylococci. This generally has been associated with prolonged courses of therapy and the presence of prosthetic materials or undrained abscesses. When antibiotic-resistant organisms are encountered in the hospital it is important to emphasize infection control policies.

PHARMACOKINETIC
Absorption
Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing. Absorption is not significantly affected by food and absorption from the oral suspension is similar to that achieved with the film-coated tablets.

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.

Biotransformation
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
Renal impairment: 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.

Hepatic impairment: 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.

Paediatric population (< 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. 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.

In paediatric patients with ventriculoperitoneal shunts who were administered linezolid 10mg/kg either 12 hourly or 8 hourly, variable cerebrospinal fluid (CSF) linezolid concentrations were observed following either single or multiple dosing of linezolid. Therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empirical treatment of paediatric patients with central nervous system infections is not recommended.

Elderly: 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.

INDICATIONS
Linezolid formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms. Linezolid is active against Gram-positive bacteria only. Linezolid has no clinical activity against Gram-negative pathogens. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected.

Vancomycin-Resistant Enterococcus faecium infections, including cases with concurrent bacteremia.

Nosocomial pneumonia caused by Staphylococcus aureus (methicillin-susceptible and -resistant strains), or Streptococcus pneumoniae (penicillin-susceptible strains). Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

Complicated skin and skin structure infections including diabetic foot infections, without concomitant osteomyelitis caused by Staphylococcus aureus (methicillin-susceptible and -resistant strains), Streptococcus pyogenes, or Streptococcus agalactiae. Linezolid has not been studied in the treatment of decubitus ulcers. Combination therapy may be clinically indicated if the documented or presumptive pathogens include Gram-negative organisms.

Uncomplicated skin and skin structure infections caused by Staphylococcus aureus (methicillin-susceptible only) or Streptococcus pyogenes.

Community-acquired pneumonia caused by Streptococcus pneumoniae (penicillin-susceptible strains only), including cases with concurrent bacteremia, or Staphylococcus aureus (methicillin-susceptible strains only).

Due to concerns about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with linezolid in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to linezolid. Therapy may be instituted empirically while awaiting the results of these tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

CONTRAINDICATIONS
Hypersensitivity to linezolid or to any of the excipients.

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.

WARNINGS AND PRECAUTIONS
Myelosuppression
Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. 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 severerenal insufficiency; receive more than 10-14 days of therapy.

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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.

Antibiotic-associated diarrhoea and 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. 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 inhibiting peristalsis are contraindicated in this situation.

Lactic acidosis
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.

Mitochondrial dysfunction
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.

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.

Peripheral and optic neuropathy
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. 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. If any patients are taking Linezolid for longer than the recommended 28 days, their visual function should be regularly monitored. If peripheral or 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.

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. Patients should be advised to inform their physician if they have a history of seizures.

Monoamine oxidase inhibitors
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.

Use with tyramine-rich foods
Patients should be advised against consuming large amounts of tyramine-rich foods (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

Superinfection
The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Special populations
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.

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk.

Impairment of fertility
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.

PREGNANCY AND LACTATION

Pregnancy
Linezolid should not be used during pregnancy unless clearly necessary i.e. only if the potential benefit outweighs the theoretical risk.

Breast-feeding
Breast-feeding should be discontinued prior to and throughout administration of linezolid.

DRUG INTERACTIONS

Monoamine oxidase inhibitors
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.

Potential interactions producing elevation of blood pressure
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. 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.

Warfarin
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.
- Care is required when giving anticoagulants with Diclofenac as it may reversibly inhibit platelet aggregation.
- Non-steroidal anti-inflammatory drugs (NSAIDs) may increase the hypoglycemic effect of antidiabetic agents; dosage adjustments of the diabetic agent may be necessary; glipizide and glyburide may not be affected as much as the other oral antidiabetic agents, however, caution with concurrent use is recommended. Diclofenac has also been reported to decrease the effects of antidiabetic agents, leading to hyperglycemia.

MAIN SIDE/ ADVERSE EFFECTS

- **Investigations:** Abnormal haematology tests, abnormal liver function tests
- **Infections and infestations:** candidiasis, vaginal candidiasis
- **Nervous system disorders:** Headache, taste alteration.
- **Eye disorders:** Optic neuropathy
- **Immune system disorders:** Anaphylaxis.
- **Metabolism and nutrition disorders:** Lactic acidosis
- **Nervous dystem disorders:** Peripheral neuropathy, convulsions
- **Skin and subcutaneous tissue disorders:** Rash, angioedema.
- **Gastrointestinal disorders:** Nausea, vomiting, diarrhoea, tongue discoloration.
- **Psychiatric disorders:** Insomnia
- **Vascular disorders:** Hypertension, transient ischaemic attacks, thrombophlebitis
- **General disorders and administration site conditions:** fatigue
- **Renal and urinary disorders:** impaired renal function, polyuria

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Patients should be warned about the potential for dizziness or symptoms of visual impairment whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs

OVERDOSE AND TREATMENT

Treatment
In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis removes approximately 30% of a dose of linezolid.

DOSAGE AND ADMINISTRATION

For oral use. Can be taken with or without food.

Infection*	Dosage And Route Of Administration		Recommended Duration of Treatment (Consecutive Days)
	Pediatric Patients[1] (Birth Through 11 Years Of Age)	Adults and Adolescents (12 Years and Older)	
Complicated skin and skin structure infections	10 mg/kg IV or orally[2] q8h	600 mg IV or orally[2] q12h	10 to 14
Community-acquired pneumonia, including concurrent bacteremia			
Nosocomial pneumonia			
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	10 mg/kg IV or orally[2] q8h	600 mg IV or orally[2] q12h	14 to 28
Uncomplicated skin and skin structure infections	<5 years: 10 mg/kg orally[2] q8h 5-11 years: 10 mg/kg orally[2] q12h	Adult: 400 mg orally[2] q12h Adolescents: 600 mg orally[2] q12h	10 to 14

* Due to the designated pathogens.

[1] Neonates <7days: Most pre-terms neonates <7 days of age (gestational age <34 weeks) have lower systematic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with a dosing regimen of 10 mg/kg q12h.
Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response.
All neonates patients should receive 10 mg/kg q8h by 7 days if life.

[2] Oral dosing using either Linezoid tablets or Linezoid for oral suspension.

Patients whose therapy is started with linezolid injection may be switched to linezolid tablets or linezolid for oral suspension, with no dosage adjustment.

Elderly patients: No dose adjustment is required.
Patients with renal insufficiency: No dose adjustment is required.

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 hemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by hemodialysis, but the concentrations of these metabolites 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 that is 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 hemodialysis).

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.

Note: The information given here is limited. For further information, consult your doctor or pharmacist.

Storage: Store below 30°C.

Presentation/Packing:
Blister pack of 1x10's per box

Product Registration Holder:
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