LINZANEXT

USP Specification

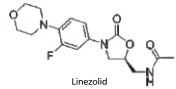
(Linezolid)

USP Specification

400mg & 600mg Film Coated Tablets

DESCRIPTION

Linzanext Tablets contain Linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for Linezolid is N-[[(5)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5 -oxazolidinyl]methyl]acetamide. Its molecular formula is $C_{16}H_{20}FN_3O_4$ and the structural formula is:



Linezolid

COMPOSITION

Linzanext (Linezolid) Tablets are available for oral administration as:
Linzanext Tablets 400mg Each film-coated tablet contains: Linezolid USP…400mg
Linzanext Tablets 600mg Each film-coated tablet contains: Linezolid USP…600mg

CLINICAL PHARMACOLOGY

Mechanism of Action

Linezolid is a synthetic, antibacterial agent belonging to the class of antibiotics, the oxazolidinones, with in-vitro activity against Gram-positive aerobic bacteria, some Gram-positive anaerobic bacteria and certain Gram-negative bacteria. It selectively inhibits bacterial protein synthesis via a mechanism of action different from that of other antibacterial agents. Linezolid binds to the 23S ribosomal RNA of the 50S subunit of the bacterial ribosome and prevents the formation of a functional 70S initiation complex which is an essential component of the bacterial translation process. The time-kill studies have shown Linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, Linezolid was found to be bactericidal for the majority of strains.

MICROBIOLOGY

Linezolid has been shown to be active against most isolates of the following microorganism, both in-vitro and in clinical infections:

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

Gram-negative aerobes

Pasteurellacanis Pasteurella multocida Resistant organisms Haemophilus influenzae Moraxella catarrhalis Neisseria species Enterobacteriaceae Pseudomonas aeruginosa

MECHANISMS OF RESISTANCE

Resistance to Linezolid is associated with point mutations in the 23S rRNA. The Linezolid resistance in these organisms is associated with a point mutation in the 23S rRNA (substitution of thymine for guanine at position 2576) of the organism. Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to Linezolid. 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.

PHARMACOKINETICS

Absorption

Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing and the absolute bioavailability is approximately 100%. Steady-state conditions are achieved by the second or third day of dosing. Effect of food Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and Cmax is decreased by about 17% when high fat food is given with Linezolid. However, the total exposure measured as AUC0-∞ values is similar under both conditions.

Distribution

Linezolid is readily distributed to well perfused tissues. Its 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 Cmax, 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 Cmax was 0.7:1.0 after multiple Linezolid dosing.

Metabolism

Metabolism Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring-opened carboxylic acid metabolites: the aminoethoxy acetic acid metabolite (A) and the hydroxyethyl glycine metabolite (B). Formation of metabolite A is presumed to be formed via an enzymatic pathway whereas metabolite B is mediated by a non-enzymatic chemical oxidation mechanism in-vitro. In-vitro studies have demonstrated that Linezolid is minimally metabolized and may be mediated by human cytochrome P450. However, the metabolic pathway of Linezolid is not fully understood.

Elimination

Nonrenal clearance accounts for approximately 65% of the total clearance of Linezolid. Under steady-state conditions, approximately 30% of the dose appears in the urine as Linezolid, 40% as metabolite B and 10% as metabolite A. The mean renal clearance of Linezolid is 40 mL/min which suggests net tubular reabsorption. Virtually no Linezolid appears in the feces, while approximately 6% of the dose appears in the feces as metabolite B and 3% as metabolite A. A small degree of nonlinearity in clearance was observed with increasing doses of Linezolid, which appears to be due to lower renal and nonrenal clearance of Linezolid at higher concentrations. However, the difference in clearance was small and was not reflected in the apparent elimination half-life.

SPECIAL POPULATION

Elderly

No dose adjustment is required.

Renal impairment

No dose adjustment is required. However, **LINZANEXT** (Linezolid) should be used with special caution in patients with severe renal insufficiency and in patients with severe renal insufficiency who are undergoing dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

Hepatic impairment

No dose adjustment is required. However, it is recommended that **LINZANEXT** (Linezolid) should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.

ADVERSE REACTIONS

Common: Diarrhoea, nausea, vomiting, headache, candidiasis, oral candidiasis, vaginal candidiasis, fungal infections, anaemia, insomnia, taste perversion (metallic taste), dizziness, hypertension, localized or general abdominal pain, constipation, dyspepsia, abnormal liver function test, increased AST, ALT or alkaline phosphatase, increased BUN, increased LDH, creatine kinase, lipase, amylase or non fasting glucose, decreased total protein, albumin, sodium or calcium, increased or decreased potassium or bicarbonate, pruritus, rash, fever, localized pain, increased neutrophils or eosinophils, decreased haemoglobin, haematocrit or red blood cell count and increased or decreased platelet or white blood cell counts.

Uncommon: Vaginitis, leucopenia, neutropenia, thrombocytopenia, eosinophilia, hyponatraemia, convulsions, hypoaesthesia, paraesthesia, blurred vision, tinnitus, arrhythmia (tachycardia), transient ischaemic attacks, phlebitis, thrombophlebitis, pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder increased total bilirubin, urticaria, dermatitis, diaphoresis, renal failure, increased creatinine, polyuria, vulvovaginal disorder, chills, fatigue, increased thirst, increased sodium or calcium, decreased non fasting glucose, increased or decreased chloride and increased reticulocyte count.

Rare: Antibiotic-associated colitis, including pseudomembranous colitis, pancytopenia, changes in visual field defect and superficial tooth discolouration.

CONTRAINDICATIONS

Linezolid is contraindicated in patients

• Who have known hypersensitivity to Linezolid or to any of the excipient of the product.

• 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.

PRECAUTIONS

Myelosuppression

Myelosuppression (including anemia, leukopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving Linezolid. In cases where the outcome is known, when Linezolid was discontinued, the affected hematologic parameters have risen toward pretreatment levels. Complete blood counts should be monitored weekly in patients who receive Linezolid, particularly in those who receive Linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression or those with a chronic infection who have received previous or concomitant antibiotic therapy. Discontinuation of therapy with Linezolid should be considered in patients who develop or have worsening myelosuppression.

Peripheral and Optic Neuropathy Peripheral and optic neuropathies

Peripheral and Optic Neuropathy Peripheral and optic neuropathies have been reported in patients treated with Linezolid, primarily in those patients treated for longer than the maximum recommended duration of 28 days. If patients experience symptoms of visual impairment, such as changes in visual acuity, changes in color vision, blurred vision or visual field defect, prompt ophthalmic evaluation is recommended. If peripheral or optic neuropathy occurs, the continued use of Linezolid in these patients should be weighed against the potential risks.

Serotonin

Serotonin Syndrome Spontaneous reports of serotonin syndrome including fatal cases associated with the co-administration of Linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Unless clinically appropriate and patients are carefully observed for signs and/or symptoms of serotonin syndrome or neuroleptic malignant syndrome-like (NMS-like) reactions, Linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, bupropion or buspirone.

Clostridium difficile Associated Diarrhea Clostridium Difficile Associated Diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Linezolid and may range in severity from mild diarrhea to fatal colitis. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of C. difficile and surgical evaluation should be instituted as clinically indicated.

Mortality imbalance

Mortality imbalance in patients with catheter-related Gram-positive bloodstream infections Linezolid should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

Lactic Acidosis Lactic acidosis has been reported with the use of Linezolid.

Patients who develop recurrent nausea or vomiting, unexplained acidosis or a low bicarbonate level while receiving Linezolid should receive immediate medical evaluation.

Convulsions

Convulsions have been reported in patients when treated with Linezolid. In some of these cases, a history of seizures or risk factors for seizures was reported.

Hypoglycemia

Post marketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with Linezolid. Diabetic patients should be cautioned of potential hypoglycemic reactions when treated with Linezolid. If hypoglycemia occurs, a decrease in the dose of insulin or oral hypoglycemic agent or discontinuation of oral hypoglycemic agent, insulin or Linezolid may be required.

Development of Drug-Resistant Bacteria

Prescribing Linezolid in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Superinfection
The effects of Linezolid therapy on normal flora have not been evaluated. The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.
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.
Pregnancy
There are no adequate and well-controlled studies in pregnant women. Linezolid should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers
Linezolid and its metabolites are excreted in the milk of lactating rats. Concentrations in milk were similar to those in maternal plasma. It is not known whether Linezolid is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Linezolid is administered to a nursing woman.
DRUG INTERACTIONS
Adrenergic Agents
Patients receiving Linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content Information. It is recommended that doses of adrenergic agents, vasopressor or dopaminergic agents, should be carefully titrated to achieve the desired response when co-administered with Linezolid.
Serotonergic Agents
Spontaneous reports of serotonin syndrome associated with co-administration of Linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported. Patients who are treated with Linezolid and concomitant serotonergic agents should be closely observed for signs and symptoms of serotonin syndrome (e.g., cognitive dysfunction, hyperpyrexia, hyperreflexia, incoordination). If any signs or symptoms occur, consider discontinuation of either one or both agents (Linezolid or concomitant serotonergic agents). If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed.
Warfarin
When warfarin was added to Linezolid therapy at steady-state, there was a 10% reduction in mean maximum international normalized ratio (INR) on coadministration with a 5% reduction in AUC INR.
OVERDOSAGE:
No specific antidote is known. No cases of overdose have been reported. However, in case of overdose 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 hemoperfusion. The two primary metabolites of Linezolid are also removed to some extent by haemodialysis.

STORAGE
Store at 20°C-25°C. Protect from light and moisture.
(excursions permitted to 15°C-30°C).
HOW SUPPLIED
LINZANEXT (Linezolid) Tablets 400mg are available in blister pack of 12's.
LINZANEXT (Linezolid) Tablets 600mg are available in blister pack of 12's.
KEEP OUT OF THE REACH OF CHILDREN.
TO BE SOLD ON PRESCRIPTION OF A REGISTERED MEDICAL PRACTITIONER ONLY.

Contains Lactose But Gluten Free

لِنزانیکسٹ

(لائنزولڈ)

400 ملی گرام، 600 ملی گرام

فلم کوٹڈ گولیاں

خوراک و ہدایات

ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

صرف مستند ڈاکٹر کے نسخہ کے مطابق ہی دوا فروخت کی جائے۔

تمام ادویات بچوں کی پہنچ سے دور رکھیں۔

دوا کو 20°C-25°C درجہ حرارت پر نمی اور روشنی سے محفوظ رکھیں۔

(درجہ حرارت کی حد 15°C سے 30°C ہے۔)

NEXT PHARMACEUTICAL
Manufactured by:
NEXT Pharmaceutical Products (Pvt.) Ltd.
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