Zyspan™

(Linezolid)

600mg/300mL
I.V. Infusion
600mg Tablets

زِسپان

(لائنزولڈ)

۶۰۰ ملی گرام/۳۰۰ ملی لیٹر آئی۔وی۔انفیوژن
۶۰۰ ملی گرام ٹیبلٹس یو۔ایس۔پی۔

QUALITATIVE AND QUANTITATIVE COMPOSITION

Zyspan™ U.S.P. Tablets 600mg

Each film-coated tablet contains: Linezolid U.S.P. 600mg

Zyspan™ I.V. Infusion 600mg/300mL

Each 300mL of solution contains: Linezolid..... 600mg

Each mL of solution contains: Linezolid..... 2mg

Innovator's Specifications

DESCRIPTION

Linezolid is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N- [[3- [3-Fluo-ro-4-(4morpholinyl) phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide. The empirical formula is $C_{16}H_{20}FN_3O_4$.

CLINICAL PHARMACOLOGY

Mechanism of Action: 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 microorganisms. 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. **Pharmacodynamics:** At both the 600 mg and 1200 mg Zyspan doses, no significant effect on QTc interval is detected at peak plasma concentration or at any other time. **Pharmacokinetics: Absorption:** Plasma linezolid Cmax and Cmin (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. **Distribution:** The plasma protein binding of linezolid is approximately 31% and is concentration independent. The volume of distribution of linezolid at steady-state averaged 40 to 50 liters in healthy adult volunteers. **Metabolism:** Linezolid is primarily metabolized by oxidation of the morpholine ring, which results in two inactive ring opened carboxylic acid metabolites: the aminoethoxyacetic 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. **Excretion:** 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.

INDICATIONS AND USAGE

Zyspan™ is an oxazolidinone class antibacterial indicated in adults and children for the treatment of the following infections caused by susceptible Gram-positive bacteria: Nosocomial pneumonia; Community-acquired pneumonia; Complicated skin and skin structure infections, including diabetic foot infections, without concomitant osteomyelitis; Uncomplicated skin and skin structure infections; Vancomycin-resistant Enterococcus faecium infections.

CONTRAINDICATIONS

Hypersensitivity: Zyspan™ formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

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

INTERACTIONS

Monoamine Oxidase Inhibitors: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase.

Adrenergic and Serotonergic Agents: Linezolid has the potential for interaction with adrenergic and serotonergic agent.
Use with tyramine-rich foods: 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).
Rifampicin: Rifampicin decreases the linezolid Cmax and AUC by a mean 21% [90% CI, 15, 27] and a mean 32% [90% CI, 27, 37], respectively. The mechanism of this interaction and its clinical significance are unknown.
Warfarin: Warfarin causes 10% reduction in mean maximum INR on co-administration with a 5% reduction in AUC INR with linezolid therapy at steady state.

USE IN SPECIFIC POPULATION

Pregnancy: Teratogenic Effects – Pregnancy Category C: Zyspan™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: Caution should be exercised when Zyspan™ is administered to a nursing woman. **Pediatric Use:** Pediatric patients exhibit wider variability in linezolid clearance and systemic exposure (AUC) compared with adults. In pediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 mcg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response.
Geriatric Use: No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.
Hepatic impairment: In severe hepatic impairment manufacturer advises use only if potential benefit outweighs risk. **Renal impairment:** Metabolites may accumulate if eGFR less than 30mL/minute/1.73m^2.

PRECAUTIONS

Myelosuppression: Discontinuation of therapy with linezolid should be considered in patients who develop or have worsening myelosuppression. **Peripheral and Optic Neuropathy:** If peripheral or optic neuropathy occurs, the continued use of Zyspan™ in these patients should be weighed against the potential risks. **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.
Mortality Imbalance in an Investigational Study in Patients with Catheter-Related Bloodstream Infections, including those with catheter-site infections: Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections. **Clostridium difficile Associated Diarrhea(CDAD):** 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. **Potential Interactions Producing Elevation of Blood Pressure:** Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents (e.g., epinephrine, norepinephrine), dopaminergic agents (e.g., dopamine, dobutamine) **Lactic Acidosis:** Lactic acidosis has been reported with the use of Zyspan™. In reported cases, patients experienced repeated episodes of nausea and vomiting. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving Zyspan™ 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:** 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 Zyspan™ 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. **Excipients:** Each ml of the solution contains 48 mg (i.e. 14.4 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 con-

tains 0.38 mg (114 mg/300 ml) sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

IMPORTANT SAFETY INFORMATION

OPTIC NEUROPATHY

Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that:

-Patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and color vision immediately;

-Patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary;

-Visual function should be monitored regularly if treatment is required for longer than 28 days.

BLOOD DISORDERS

Hematopoietic disorders (including thrombocytopenia, anemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:

-receive treatment for more than 10-14days;

-have pre-existing myelosuppression;

-are receiving drugs that may have adverse effects on hemoglobin, blood counts, or platelet function;

-have severe renal impairment.

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

ADVERSE REACTIONS

GENERAL SIDE EFFECTS: -Very common: Diarrhea, eosinophilia, headache, nausea, taste disturbances, vomiting **-Uncommon:** Abdominal pain, blurred vision, constipation, diaphoresis, dizziness, dry mouth, dyspepsia, electrolyte disturbances, fatigue, fever, gastritis, glossitis, hypertension, hypoesthesia, insomnia, leucopenia, pancreatitis, paresthesia, polyuria, pruritus, rash, stomatitis, thirst, thrombocytopenia, tinnitus, tongue discoloration. **-Rare:** Renal failure, tachycardia, transient ischemic attacks. **-Frequency not known:** Anemia, antibiotic-associated colitis, convulsions, hyponatremia, lactic acidosis, optic neuropathy reported on prolonged therapy, pancytopenia, peripheral neuropathy reported on prolonged therapy, Stevens-Johnson syndrome, tooth discoloration, toxic epidermal necrolysis.

SPECIFIC SIDE EFFECTS:

Uncommon: with intravenous use: Injection site reactions.

DOSAGE AND ADMINISTRATION

General Dosage and Administration: The recommended dosage for Zyspan™ formulations for the treatment of infections is described as under.

	Dosage, Route, and Frequency of Administration		
Infection	**Pediatric Patients (Birth through 11years of Age)**	**Adults and Adolescents (12 years and Older)**	**Duration (days)**
Nosocomial pneumonia	10 mg/kg intravenously or oral‡ every 8 hours	600 mg intravenously or oral‡ every 12 hours	10 to 14
Community-acquired pneumonia, including concurrent bacteremia			
Complicated skin and skin structure infections			
Vancomycin resistant Enterococcus faecium infections, including concurrent bacteremia	10 mg/kg intravenously or oral‡ every 8 hours	600 mg intravenously or oral‡ every 12 hours	14 to 28
Uncomplicated skin and skin structure infections	less than 5 yrs: 10 mg/kg oral‡ every 8 hours 5-11 yrs: 10 mg/kg oral‡ every 12 hours	Adults: 400 mg oral‡ every 12 hours Adolescents: 600 mg oral‡ every 12 hours	10 to 14

* Due to the designated pathogens

† Neonates less than 7 days: Most pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have lower systemic 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 every 12 hours. Consideration may be given to the use of 10 mg/kg every 8 hours regi-

men in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg every 8 hours by 7 days of life. ‡ Oral dosing using either Zyspan™ Tablets or Zyspan™ for Oral Suspension. No dose adjustment is necessary when switching from intravenous to oral administration. **Intravenous Administration:** Zyspan™ I.V. should be administered by intravenous infusion over a period of 30 to 120 minutes. Additives should not be introduced into this solution. If Zyspan™ I.V. is to be given concomitantly with another drug, each drug should be given separately in accordance with the recommended dosage and route of administration for each product. If the same intravenous line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of Zyspan™ I.V. with an infusion solution compatible with Zyspan™ I.V. Injection and with any other drug(s) administered via this common line. Compatible intravenous solutions include 0.9% Sodium Chloride Injection, U.S.P., 5% Dextrose Injection, U.S.P., and Lactated Ringer's Injection, U.S.P. Physical incompatibilities resulted when Zyspan™ I.V. Injection was combined with the following drugs during simulated Y-site. Administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isothionate, erythromycin lactobionate, phenytoin sodium, and trimethoprim-sulfamethoxazole. Additionally, chemical incompatibility resulted when Zyspan™ I.V. Injection was combined with ceftriaxone sodium.

OVERDOSAGE

In the event of overdosage, supportive care is advised, with maintenance of glomerular filtration. Hemodialysis may facilitate more rapid elimination of linezolid. Data are not available for removal of linezolid with peritoneal dialysis or hemoperfusion.

DOSAGE: As directed by the physician.

INSTRUCTIONS

For Tablets: Store below 30°C. Protect from heat, light & moisture.
For Infusion: Store at 25°C, excursions permitted to 15°C - 30°C.
Protect from sunlight. Do not freeze. Discard unused portion. Infusion should not be used if container is leaking, solution is cloudy or it contains undissolved particles. Keep infusion in unit carton until ready to use. Infusion may exhibit a yellow colour that intensifies over time,with no adverse effect on potency. Keep all medicines out of the reach of children. For Intravenous Use Only. To be sold on the prescription of a registered medical practitioner only.

PRESENTATION

Zyspan™ (Linezolid) Tablets 600mg are available in ALU/ALU blister pack of 2x6's.
Zyspan™ (Linezolid) I.V. Infusion 600mg/300mL is available in 300mL glass vial.

علامات/طریقہ استعمال:

ذِسپان نوسوکومیل انفیکشن، کمیونٹی اکوائرڈ نمونیا، جلد کے پیچیدہ انفیکشنز، ذیابیطس کے مریضوں میں ڈائیبٹک فٹ اور جن مریضوں کو ونکومائسن سے مزاحمت ہو، ان کے علاج کے لیے تجویز کردہ ہے۔

ذِسپان ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

مضر اثرات: دست، اسینوفلز کی مقدار کا بڑھنا، سر درد، متلی، الٹی، منہ کا ذائقہ خراب ہونا، دھندلا پن، غنودگی۔

احتیاطی تدابیر: حاملہ خواتین اور دودھ پلانے والی مائیں ضرورت پڑنے کے پیش نظر صرف ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔ سوڈیم کنٹرولڈ ڈائیٹ کے مریض احتیاط سے استعمال کریں۔

کلوسٹریڈیم ڈیفیسائل سے منسلک ڈائریا کا خدشہ ہوتے ہی ذِسپان کا استعمال روک دیں۔ لِنز ولڈ کے استعمال کے دوران ان کنٹرولڈ بی پی کے مریضوں میں بی پی کی نگرانی کرنا نہایت ضروری ہے۔

جن مریضوں میں بی پی کنٹرول نہ ہو اُن میں لِنز ولڈ کا استعمال ممنوع ہے۔

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔

ہدایات: ٹیبلٹس کے لیے: ۳۰ ڈگری سینٹی گریڈ سے کم پر رکھیں۔ روشنی، گرمی اور نمی سے محفوظ رکھیں۔

انفیوژن کے لیے: ۲۵ ڈگری سینٹی گریڈ پر رکھیں، محفوظ رکھنے کی حد ۱۵ سے ۳۰ ڈگری سینٹی گریڈ ہے۔

سورج کی روشنی سے محفوظ رکھیں۔ منجمد ہونے سے بچائیں۔ غیر استعمال شدہ محلول کو ضائع کر دیں۔

انفیوژن کے لیک ہونے، دُھندلا ہونے یا اس میں کوئی غیر حل پذیر شے نظر آنے کی صورت میں

ہرگز استعمال نہ کریں۔ انفیوژن کو استعمال سے قبل ہی کارٹن سے نکالیں۔

انفیوژن کا رنگ وقت گزرنے کے ساتھ ساتھ پیلا ہو سکتا ہے جس کا انفیوژن کی افادیت پر کوئی اثر نہیں ہوتا۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔ صرف وریدی استعمال کیلئے۔

For detailed information:

Genix Pharma (Pvt.) Ltd.

44,45-B, Korangi Creek Road, Karachi-75190, Pakistan.
UAN: +92-21-111-10-10-11, **Email:** info@genixpharma.com
www.genixpharma.com

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