For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Linezolid I.V. injection 2 mg/ml

Linespan

COMPOSITION
Linespan 100ml/ 300ml I.V
Each 100 ml contains
Linezolid ..... 200 mg
Dextrose BP ..... 5% w/v
Water for injection BP ..... q.s.

PHARMACOLOGY

Pharmacodynamics
Linezolid is a synthetic antibacterial agent of a new class of antibiotics, the oxazolidinones, which has clinical utility in the treatment of infections caused by aerobic gram-positive bacteria. Linezolid inhibits bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents; therefore, cross-resistance between linezolid and other classes of antibiotics is unlikely. The results of 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.

Linezolid has been shown to be active against most isolates of the following microorganisms, both *in vitro* and in clinical infections.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecium (vancomycin-resistant strains only)
Staphylococcus aureus (including methicillin-resistant strains)
Streptococcus agalactiae
Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP] *)
Streptococcus pyogenes
*MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.
The following *in vitro* data are available, but their clinical significance is unknown . At least 90% of the following microorganisms exhibit an *in vitro* minimum inhibitory concentration (MIC) less than or equal to the susceptible breakpoint for linezolid. However, the safety and effectiveness of linezolid in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and facultative Gram-positive microorganisms
Enterococcus faecalis (including vancomycin-resistant strains)
Enterococcus faecium (vancomycin-susceptible strains)
Staphylococcus epidermidis (including methicillin-resistant strains)
Staphylococcus haemolyticus
Viridans group streptococci

Aerobic and facultative Gram-negative microorganisms
Pasteurella multocida

Pharmacokinetics
Absorption: Linezolid is rapidly and extensively absorbed after oral dosing. Maximum plasma concentrations are reached approximately 1 to 2 hours after dosing, and the absolute bioavailability is approximately 100%. Therefore, linezolid may be given orally or intravenously without dose adjustment.
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 C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as $AUC_{0-(infinity)}$ values is similar under both conditions.

Distribution: Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well-perfused tissues. 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 litres in healthy adult volunteers.

Linezolid concentrations have been determined in various fluids from a limited number of subjects in Phase 1 volunteer studies following multiple dosing of linezolid. The ratio of linezolid in saliva relative to plasma was 1.2 to 1 and for sweat relative to plasma was 0.55 to 1.

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 B is mediated by a non-enzymatic chemical oxidation mechanism *in vitro*. Linezolid is not an inducer of cytochrome P450 (CYP) in rats, and it has been demonstrated from *in vitro* studies that linezolid is not detectably metabolized by human cytochrome P450 and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4).

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 renal clearance of linezolid is low (average 40 mL/min) and suggests net tubular reabsorption. Virtually no linezolid appears in the faeces, while approximately 6% of the dose appears in the faeces 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.

INDICATIONS
Linespan formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms.

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

Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains [MDRSP]). 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.* It 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* (including multi-drug resistant strains [MDRSP] *), including cases with concurrent bacteremia, or *Staphylococcus aureus* (methicillin-susceptible strains only).
To reduce the development of drug-resistant bacteria and maintain the effectiveness of linezolid and other antibacterial drugs, linezolid should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

*MDRSP refers to isolates resistant to two or more of the following antibiotics: penicillin, second-generation cephalosporins, macrolides, tetracycline, and trimethoprim/sulfamethoxazole.

DOSAGE AND ADMINISTRATION
The recommended dosage for linezolid formulations for the treatment of infections is described below. Doses of linezolid are administered every twelve hours.

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	Dosage Guidelines for Linezolid		
Infection *	**Dosage and Route of Administration**		**Recommended Duration of Treatment (consecutive days)**
	Paediatric Patients **/* (Birth through 11 Years of Age)	**Adults and Adolescents (12 Years and Older)**	
Complicated skin and skin structure infections Community-acquired pneumonia, including concurrent bacteremia	10 mg/kg IV q8h	600 mg IV q12h	10 to 14
Nosocomial pneumonia			
Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteremia	10 mg/kg IV q8h	600 mg IV q12h	14 to 28
* Due to the designated pathogens .			
/* **Neonates <7 days: Most pre-term neonates < 7 days of age (gestational age < 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 q12h. Consideration may be given to the use of 10 mg/kg q8h regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg q8h by 7 days of life.			

Patients with infection due to MRSA should be treated with linezolid 600 mg q12h.
No dose adjustment is necessary when switching from intravenous to oral administration. Patients whose therapy is started with linezolid I.V. Injection may be switched to linezolid tablets at the discretion of the physician, when clinically indicated.

Intravenous Administration
Linezolid I.V. injection is supplied in single-use, ready-to-use infusion bags. Parenteral drug products should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired.

Linezoid I.V. injection should be administered by intravenous infusion over a period of 30 to 120 minutes. **Do not use this intravenous infusion bag in series connections.** Additives should not be introduced into this solution. If linezolid I.V. Injection 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 Linezolid I.V. injection with an infusion solution compatible with linezolid I.V. injection and with any other drug(s) administered via this common line.

Compatible Intravenous Solutions
5% Dextrose Injection, USP
0.9% Sodium Chloride Injection, USP
Lactated Ringer's Injection, USP

CONTRAINDICATIONS
Linezolid formulations are contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components.

WARNINGS AND PRECAUTIONS
Pseudomembranous colitis has been reported with nearly all antibacterial agents, including linezolid and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent.
Thrombocytopenia has been reported in patients receiving linezolid. Platelet counts should be monitored in patients who are at increased risk for bleeding.

Patients should be advised that:
- Linezolid may be taken with or without food.
- They should inform their physician if they have a history of hypertension.
- Large quantities of foods or beverages with high tyramine content should be avoided while taking linezolid. Quantities of tyramine consumed should be less than 100 mg per meal.

Drug Interactions
Monoamine Oxidase Inhibition: Linezolid is a reversible, nonselective inhibitor of monoamine oxidase. Therefore, linezolid has the potential for interaction with adrenergic and serotonergic agents.

Adrenergic Agents: Some individuals receiving Linezolid may experience a reversible enhancement of the pressor response to indirect-acting sympathomimetic agents, vasopressor or dopaminergic agents. Commonly used drugs such as phenylpropanolamine and pseudoephedrine have been specifically studied. Initial doses of adrenergic agents, such as dopamine or epinephrine, should be reduced and titrated to achieve the desired response.

Serotonergic Agents: Co-administration of linezolid and serotonergic agents was not associated with serotonin syndrome in phase 1, 2 or 3 studies. Since there is limited experience with concomitant administration of linezolid and serotonergic agents, physicians should be alert to the possibility of signs and symptoms of serotonin syndrome (e.g., hyperpyrexia, and cognitive dysfunction) in patients receiving such concomitant therapy.
Renal Impairment
No dose adjustment is required for patients with renal impairment.

Hepatic Impairment
No dose adjustment is required for patients with mild to moderate hepatic insufficiency.

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 foetus.

Lactation
Linezolid and its metabolites are excreted in human milk. Caution should be exercised when linezolid is administered to a nursing woman.

Paediatric use
Please refer under **DOSAGE and ADMINISTRATION** section.

Geriatric use
No dosage adjustments are required in geriatric group with infections due to susceptible organisms.

UNDESIRABLE EFFECTS
The most common adverse events reported with linezolid are:
Diarrhoea, headache, nausea. Other adverse events reported are: oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus and tongue discolouration. Thrombocytopenia is dependent on duration of therapy. Other effects include mild derrangements in hepatic enzymes.

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

INCOMPATIBILITY
Physical incompatibilities resulted when linezolid 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 linezolid I.V. Injection was combined with ceftriaxone sodium.

Storage
Store below 30°C. Protect from light. Do not freeze.

Presentation
Linespan Bottle of 100ml/300ml

Cipla

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