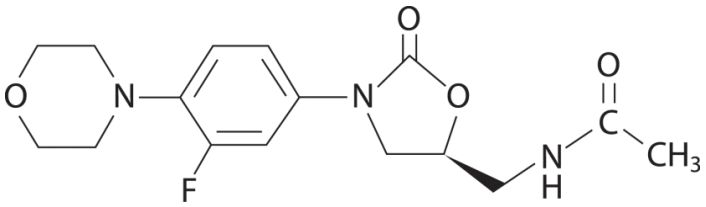
LINEZOLID I.V. 200mg/100ml and 600mg/300ml

NIRZOLID®* I.V. INJECTION

Each 100 mL Contains:
Linezolid IP 200 mg
Dextrose IP (As Anhydrous) 5% w/v
Water for Injections IP q. s.

DESCRIPTION:
NIRZOLID®* I.V. Injection contains linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide.The empirical formula is $C_{16}H_{20}FN_3O_4$. Its molecular weight is 337.35, and its chemical structure is represented below:



NIRZOLID®* I.V. Injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each mL contains 2 mg of linezolid. Inactive ingredients are Sodium Citrate, Citric Acid, and Glucose in an aqueous vehicle for intravenous administration. The sodium (Na+) content is 0.422 mg/ml.

CLINICAL PHARMACOLOGY:
Pharmacokinetics
The mean pharmacokinetic parameters of linezolid in adults after intravenous (IV) doses are summarized in Table 1. Plasma concentrations of linezolid at steady-state after dose of 600 mg given every 12 hours (q12h) are shown in table-1.
Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults
Table 1. Mean (Standard Deviation) Pharmacokinetic Parameters of Linezolid in Adults

Dose of Linezolid	**C_{max} µg/mL**	**C_{min} µg/mL**	**T_{max} hrs**	**AUC* µg·h/mL**	**t½ hrs**	**CL mL/min**
600 mg IV injection						
single dose	12.90 (1.60)	-----	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
every 12 hours	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)

‡ Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.
Cmax= Maximum plasma concentration; Cmm= Mimimum plasma concentration; Tmax= Time to Cmax; AUC= Area under concentration-time curve; t½= Elimination half-life; CL= Systemic clearance

Absorption: 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 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 readily distributes to well-perfused tissues. The plasma protein binding of linezolid is approximately 31% and is concentration-independent.
As per literature, the ratio of linezolid in saliva relative to plasma is 1.2 to 1 and for sweat relative to plasma is 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).

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 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 Populations
Geriatric: The pharmacokinetics of linezolid are not significantly altered in elderly patients (65 years or older). Therefore, dose adjustment for geriatric patients is not necessary.

Pediatric:
After administration of single IV doses. The Cmax and the volume of distribution (Vss) of linezolid are similar regardless of age in pediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from >1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of pediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values approach those observed for the adult population. There is wider inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all pediatric age groups as compared with adults.
Similar mean daily AUC values were observed in pediatric patients from birth to 11 years of age dosed every 8 hours (q8h) relative to adolescents or adults dosed every 12 hours (q12h). Therefore, the dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h (see **DOSAGE AND ADMINISTRATION**).

Gender: Females have a slightly lower volume of distribution of linezolid than males. Plasma concentrations are higher in females than in males, which is partly due to body weight differences. There are no significant gender differences in mean apparent elimination-rate constant or half-life. Thus, drug exposure in females is not expected to substantially increase beyond levels known to be well tolerated. Therefore, dose adjustment by gender does not appear to be necessary.

Renal Insufficiency: Linezolid, are not altered in patients with any degree of renal insufficiency. As per references approximately 30% of a dose was eliminated in a 3-hour dialysis session beginning 3 hours after the dose of linezolid was administered; therefore, linezolid should be given after hemodialysis.

Hepatic Insufficiency: The pharmacokinetics of linezolid are not altered in patients (n=7) with mild-to-moderate hepatic insufficiency (Child-Pugh class A or B). On the basis of the available information, no dose adjustment is recommended for patients with mild-to-moderate hepatic insufficiency. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency has not been evaluated.

MICROBIOLOGY:
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. The in vitro spectrum of activity of linezolid also includes certain Gram-negative bacteria and anaerobic 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. Linezolid binds to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process. 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.

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

As per references, 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

INDICATIONS AND USAGE:
NIRZOLID®* Injection is indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms. Linezolid is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected. (See WARNINGS)

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]).

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.

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.

CONTRAINDICATIONS:
Linezolid is 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.

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). (See **PRECAUTIONS, Drug Interactions**).

Potential Serotonergic Interactions - Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, 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 or buspirone. (See **PRECAUTIONS, General and Drug Interactions**).

WARNINGS:

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.

Linezolid is not approved and should not be used for the treatment of patients with catheter-related bloodstream infections or catheter-site infections.

Linezolid has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see INDICATIONS).

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. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use.

Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

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.

PRECAUTIONS:

General

Lactic Acidosis - Lactic acidosis has been reported with the use of Linezolid. 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 Linezolid should receive immediate medical evaluation.

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 (see **PRECAUTIONS, Drug Interactions**).

Where administration of Linezolid and concomitant serotonergic agents is clinically appropriate, 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 discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed (see package insert of the specified agent(s) for a description of the associated discontinuation symptoms).

Peripheral and Optic Neuropathy - Peripheral and optic neuropathy have been reported in patients treated with Linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with Linezolid for less than 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. **Visual function should be monitored in all patients taking linezolid for extended periods (≥ 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with linezolid**. If peripheral or optic neuropathy occurs, the continued use of linezolid in these patients should be weighed against the potential risks.

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.
The use of antibiotics may promote the overgrowth of nonsusceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.
Linezolid has not been studied in patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or untreated hyperthyroidism.
The safety and efficacy of Linezolid formulations given for longer than 28 days have not been evaluated in controlled clinical trials.
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.

Drug-Drug Interactions
Drugs Metabolized by Cytochrome P450:
Linezolid is not an inducer of cytochrome P450 (CYP) in rats. It 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). Therefore, no CYP450-induced drug interactions are expected with linezolid. Concurrent administration of linezolid does not substantially alter the pharmacokinetic characteristics of (S) warfarin, which is extensively metabolized by CYP2C9. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Antibiotics:
Aztreonam: The pharmacokinetics of linezolid or aztreonam are not altered when administered together.

Gentamicin: The pharmacokinetics of linezolid or gentamicin are not altered when administered together.

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: A significant pressor response has been observed in normal adult subjects receiving linezolid and tyramine doses of more than 100 mg. Therefore, patients receiving linezolid need to avoid consuming large amounts of foods or beverages with high tyramine content.
As per literature a reversible enhancement of the pressor response of either pseudoephedrine HCl (PSE) or phenylpropanolamine HCl (PPA) is observed when linezolid is administered to healthy normotensive subjects (see **PRECAUTIONS, Drug Interactions**).

Serotonergic Agents: No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis, hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

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Carcinogenesis, Mutagenesis, Impairment of Fertility
Linezolid did not affect the fertility or reproductive performance of adult female rats. It reversibly decreased fertility and reproductive performance in adult male rats when given at doses ≥ 50 mg/kg/day, with exposures approximately equal to or greater than the expected human exposure level (exposure comparisons are based on AUCs). The reversible fertility effects were mediated through altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. Epithelial cell hypertrophy and hyperplasia in the epididymis was observed in conjunction with decreased fertility. Similar epididymal changes were not seen in dogs.

Pregnancy
Teratogenic Effects. Pregnancy Category C: Linezolid was not teratogenic in mice, rats, or rabbits at exposure levels 6.5-fold (in mice), equivalent to (in rats), or 0.06-fold (in rabbits) the expected human exposure level, based on AUCs. However, embryo and fetal toxicities were seen. 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.

Pediatric Use
The use of linezolid for the empiric treatment of pediatric patients with central nervous system infections is not recommended.
The dosage for pediatric patients up to 11 years of age should be 10 mg/kg q8h. Pediatric patients 12 years and older should receive 600 mg q12h.
Pre-term neonates should be initiated with a dosing regimen of 10 mg/kg q12h. Consideration may be given to the use of a 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 (see DOSAGE AND ADMINISTRATION).

Geriatric Use
No differences in safety or effectiveness were observed between geriatric patients and younger patients.

ADVERSE REACTIONS:
Adult Patients
The most common adverse events in patients treated with Linezolid were diarrhea, headache, vomiting and nausea, other adverse events reported are taste alteration, oral moniliasis, vaginal moniliasis, hypertension, dyspepsia, localized abdominal pain, pruritus, fungal infection, abnormal liver function, dizziness, and tongue discoloration in 1% of adult patients.

Pediatric Patients
Following adverse events reported in at least 2% of pediatric patients treated with linezolid. Fever, diarrhea, vomiting, sepsis, rash, headache, anemia, thrombocytopenia, upper respiratory infection, nausea, dyspnea, reaction at site of injection or of vascular catheter, trauma, Pharyngitis, convulsion, hypokalemia, pneumonia, cough, generalized abdominal pain, localized abdominal pain, apnea, gastrointestinal bleeding, generalized edema, loose stools, localized pain, skin disorder.

Following adverse events reported in more than 1% of pediatric patients are as follows.
Diarrhea, nausea, headache, loose stools, thrombocytopenia, vomiting, generalized abdominal pain, localized abdominal pain, anemia, rash.

Laboratory Changes
Thrombocytopenia associated with the use of Linezolid appears to be dependent on duration of therapy, (generally greater than 2 weeks of treatment). Bleeding may occur in thrombocytopenic patients. (See **WARNINGS**)

DOSAGE AND ADMINISTRATION:

Infection*	**Dosage and Route of Administration**		**Recommended Duration of Treatment (consecutive days)**
	Pediatric 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 Nosocomial pneumonia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	10 to 14
Vancomycin-resistant Enterococcus faecium infections, including concurrent bacteremia	10 mg/kg IV or oral‡ q8h	600 mg IV or oral‡ q12h	14 to 28
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral‡ q8h	Adults: 400 mg oral‡ q12h	10 to 14

	5-11 yrs: 10 mg/kg oral‡ q12h	Adolescents: 600 mg oral‡ q12h	

‡ Due to the designated pathogens (see **INDICATIONS AND USAGE**)

† 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.

Adult patients with infection due to MRSA should be treated with Linezolid 600 mg q12h.
However, 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 µg/mL, lower systemic exposure, site and severity of infection, and the underlying medical condition should be considered when assessing clinical response (**see CLINICAL PHARMACOLOGY, Special Populations, Pediatric and PRECAUTIONS, Pediatric Use**).

Total treatment duration was determined by the treating physician based on site and severity of the infection, and on the patient's clinical response.
No dose adjustment is necessary when switching from intravenous to oral administration.

Intravenous Administration
NIRZOLID®* I.V. Injection is supplied in single-use, ready-to-use infusion bottle. Parenteral drug products should be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bottle. If leaks are detected, discard the solution, as sterility may be impaired.
NIRZOLID®* I.V. Injection should be administered by intravenous infusion over a period of 30 to 120 minutes. Do not use this intravenous infusion bottle in series connections. Additives should not be introduced into this solution. If NIRZOLID®* 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. In particular, physical incompatibilities resulted when NIRZOLID®* 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 NIRZOLID®* I.V. Injection was combined with ceftriaxone sodium.
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 (see Compatible Intravenous Solutions).

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

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.

STORAGE:
Keep the infusion bottle in the overwrap until ready to use. Store at room temperature. Protect from freezing. Nirzolid I.V. Injection may exhibit a yellow color that can intensify over time without adversely affecting potency.

KEEP MEDICINE OUT OF REACH OF CHILDREN

PRESENTATION:
100 mL Bottle (200 mg Linezolid)
300 mL Bottle (600 mg Linezolid)

ACULIFE®
Manufactured in India by:
Aculife Healthcare Pvt. Ltd.
Sachana, Gujarat 382150, India.
* TM owners-Nirma Ltd.