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

LINOX IV

1. Generic Name

Linezolid I.V. Injection 2mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 300 ml Contains

Linezolid I.P. ….....600 mg

Dextrose (Anhydrous) I.P...5.0% w/v

Water for Injections I.P...…q.s.

The Excipients used are Dextrose (Anhydrous), Sodium citrate, Citric acid (Monohydrate), Sodium Hydroxide, Hydrochloric acid and Water for Injection.

3. Dosage Form and Strength

Dosage Form: Injection

Strength : 2mg/ml

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For the treatment of Complicated/uncomplicated skin & skin structure infections/community acquired pneumonia.

4.2 Posology and Method of Administration

Dosage: As directed by the Physician.

Posology

LINOX IV solution for infusion, film-coated tablets or oral suspension may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to either oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as linezolid has an oral bioavailability of approximately 100%.

Recommended dosage and duration of treatment for adults:

The duration of treatment is dependent on the pathogen, the site of infection and its severity, and on the patient's clinical response.

The following recommendations for duration of therapy reflect those used in the clinical trials. Shorter treatment regimens may be suitable for some types of infection but have not been evaluated in clinical trials.

The maximum treatment duration is 28 days. The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.

No increase in the recommended dosage or duration of treatment is required for infections associated with concurrent bacteraemia.

The dose recommendation for the solution for infusion and the tablets/granules for oral suspension are identical and are as follows:

Infections	**Dosage**	**Duration of treatment**
Nosocomial pneumonia	600 mg twice daily	10-14 Consecutive days
Community acquired pneumonia		
Complicated skin and soft tissue infections	600 mg twice daily	

Paediatric population:

The safety and efficacy of linezolid in children aged (< 18 years old) has not been established.

Elderly:

No dose adjustment is required.

Renal impairment:

No dose adjustment is required.

Severe renal impairment (i.e. CL_{CR} < 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 haemodialysis, linezolid should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are removed to some extent by haemodialysis, 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 who are 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 haemodialysis).

Hepatic impairment:

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.

Method of administration:

The recommended linezolid dosage should be administered intravenously twice daily.

Route of administration: Intravenous use.

The solution for infusion should be administered over a period of 30 to 120 minutes.

4.3 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-HT_1 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.

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration.

4.4 Special Warnings and Precautions for Use

Myelosuppression

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, when linezolid was discontinued, the affected haematologic parameters have risen toward pretreatment levels. The risk of these effects appears to be related to the duration of treatment. 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 severe renal insufficiency; receive more than 10-14 days of therapy. 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.

In addition, it is recommended that complete blood counts (including haemoglobin levels, platelets, and total and differentiated leucocyte counts) should be monitored weekly in patients who receive linezolid regardless of baseline blood count.

In compassionate use studies, a higher incidence of serious anaemia was reported in patients receiving linezolid for more than the maximum recommended duration of 28 days. These patients more often required blood transfusion. Cases of anaemia requiring blood transfusion have also been reported post marketing, with more cases occurring in patients who received linezolid therapy for more than 28 days.

Cases of sideroblastic anaemia have been reported post-marketing. Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered following discontinuation of linezolid with or without treatment for their anaemia.

Mortality imbalance in a clinical trial in patients with catheter-related Gram positive bloodstream infections

Excess mortality was seen in patients treated with linezolid, relative to vancomycin/dicloxacillin/oxacillin, in an open-label study in seriously ill patients with intravascular catheter-related infections [78/363 (21.5%) vs 58/363 (16.0%)]. The main factor influencing the mortality rate was the Gram positive infection status at baseline. Mortality rates were similar in patients with infections caused purely by Gram positive organisms (odds ratio 0.96; 95% confidence interval: 0.58-1.59) but were significantly higher (p=0.0162) in the linezolid arm in patients with any other pathogen or no pathogen at baseline (odds ratio 2.48; 95% confidence interval: 1.38-4.46). The greatest imbalance occurred during treatment and within 7 days following discontinuation of study drug. More patients in the linezolid arm acquired Gram negative pathogens during the study and died from infection caused by Gram negative pathogens and polymicrobial infections. Therefore, in complicated skin and soft tissue infections linezolid should only be used in patients with known or possible co-infection with Gram negative organisms if there are no alternative treatment options available. In these circumstances treatment against Gram negative organisms must be initiated concomitantly.

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. Therefore, it is important to consider this diagnosis in patients who develop serious diarrhoea during or after the use of linezolid. 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 LINOX IV; 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. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary. If any patients are taking LINOX IV for longer than the recommended 28 days, their visual function should be regularly monitored.

If peripheral or optic neuropathy occurs, the continued use of LINOX IV 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 LINOX IV. 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.

Superinfection

The effects of linezolid therapy on normal flora have not been evaluated in clinical trials.

The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. For example, approximately 3% of patients receiving the recommended linezolid doses experienced drug-related candidiasis during clinical trials. 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.

Clinical trials

The safety and effectiveness of linezolid when administered for periods longer than 28 days have not been established.

Controlled clinical trials did not include patients with diabetic foot lesions, decubitus or ischaemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

Excipients

Each ml of the solution contains 45.7 mg (i.e. 13.7 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 contains 0.38 mg (114 mg/300 ml) sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

4.5 Drugs 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 of the order of 30-40 mmHg, compared with 11-15 mmHg increases with linezolid alone, 14-18 mmHg with either pseudoephedrine or phenylpropanolamine alone and 8-11 mmHg with placebo. Similar studies in hypertensive subjects have not been conducted. 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.

Potential serotonergic interactions

The potential drug-drug interaction with dextromethorphan was studied in healthy volunteers. Subjects were administered dextromethorphan (two 20 mg doses given 4 hours apart) with or without linezolid. No serotonin syndrome effects (confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) have been observed in normal subjects receiving linezolid and dextromethorphan.

Post marketing experience: there has been one report of a patient experiencing serotonin syndrome-like effects while taking linezolid and dextromethorphan which resolved on discontinuation of both medications.

During clinical use of linezolid with serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), cases of serotonin syndrome have been

reported. Therefore, while co-administration is contraindicated, management of patients for whom treatment with linezolid and serotonergic agents is essential.

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).

Drugs metabolised by cytochrome P450

Linezolid is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not inhibit any of the clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Similarly, linezolid does not induce P450 isoenzymes in rats. Therefore, no CYP450-induced drug interactions are expected with linezolid.

Rifampicin

The effect of rifampicin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased 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

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. There are insufficient data from patients who have received warfarin and linezolid to assess the clinical significance, if any, of these findings.

4.6 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

There are limited data from the use of linezolid in pregnant women. Studies in animals have shown reproductive toxicity. A potential risk for humans exists.

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

Breast-feeding

Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breast-feeding should be discontinued prior to and throughout administration.

Fertility

In animal studies, linezolid caused a reduction in fertility.

4.7 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.

4.8 Undesirable Effects

The table below provides a listing of adverse drug reactions with frequency based on all-causality data from clinical studies that enrolled more than 2,000 adult patients who received the recommended linezolid doses for up to 28 days.

Those most commonly reported were diarrhoea (8.4%), headache (6.5%), nausea (6.3%) and vomiting (4.0%).

The most commonly reported drug-related adverse events which led to discontinuation of treatment were headache, diarrhoea, nausea and vomiting. About 3% of patients discontinued treatment because they experienced a drug-related adverse event.

Additional adverse reactions reported from post-marketing experience are included in the table with frequency category 'Not known', since the actual frequency cannot be estimated from the available data.

The following undesirable effects have been observed and reported during treatment with linezolid with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); Not known (cannot be estimated from the available data)

System Organ Class	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1,000 to <1/100)**	**Rare (≥1/10,000 to <1/1,000)**	**Very Rare (<1/10,000)**	**Frequency not known (cannot be estimated from available data)**
Infections and infestations	candidiasis, oral candidiasis, vaginal candidiasis, fungal infections	vaginitis	antibiotic-associated colitis, including pseudomembranous colitis*		
Blood and the lymphatic system disorders	anaemia*†	leucopenia*, neutropenia, thrombocytopenia*, eosinophilia	pancytopenia*		myelosuppression* , sideroblastic anaemia*
Immune system disorders					anaphylaxis
Metabolism and nutrition disorders		hyponatraemia			lactic acidosis*
Psychiatric disorders	insomnia				
Nervous system disorders	headache, taste perversion (metallic	convulsions*, hypoaesthesia, paraesthesia			serotonin syndrome**, peripheral neuropathy*

	taste), dizziness				
Eye disorders		blurred vision*	changes in visual field defect*		optic neuropathy*, optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
Ear and labyrinth disorders		tinnitus			
Cardiac disorders		arrhythmia (tachycardia)			
Vascular disorders	hypertension	transient ischaemic attacks, phlebitis, thrombophlebitis			
Gastrointestinal disorders	diarrhoea, nausea, vomiting, localised or general abdominal pain, constipation, dyspepsia	pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder	superficial tooth discolouration		
Hepato-biliary disorders	abnormal liver function test; increased AST, ALT or alkaline phosphatase	increased total bilirubin			
Skin and subcutaneous tissue disorders	pruritus, rash	urticaria, dermatitis, diaphoresis			bullous disorders such as those described as Stevens-Johnson syndrome and

					toxic epidermal necrolysis, angioedema, alopecia
Renal and urinary disorders	increased BUN	renal failure, increased creatinine, polyuria			
Reproductive system and breast disorders		vulvovaginal disorder			
General disorders and administration site conditions	fever, localised pain	chills, fatigue, injection site pain, increased thirst			
Investigations	Chemistry Increased LDH, creatine kinase, lipase, amylase or non-fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate. Haematology Increased neutrophils or	Chemistry Increased sodium or calcium. Decreased non fasting glucose. Increased or decreased chloride. Haematology Increased reticulocyte count. Decreased neutrophils.			

	eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.				

* See Special warnings and precautions for use.

** See Contraindications and Interaction with other medicinal products and other forms of interaction

† See below

The following adverse reactions to linezolid were considered to be serious in rare cases: localised abdominal pain, transient ischaemic attacks and hypertension.

†In controlled clinical trials where linezolid was administered for up to 28 days, 2.0% of the patients reported anaemia. In a compassionate use program of patients with life-threatening infections and underlying co-morbidities, the percentage of patients who developed anaemia when receiving linezolid for ≤ 28 days was 2.5% (33/1326) as compared with 12.3% (53/430) when treated for >28 days. The proportion of cases reporting drug-related serious anaemia and requiring blood transfusion was 9% (3/33) in patients treated for ≤ 28 days and 15% (8/53) in those treated for >28 days.

Paediatric population

Safety data from clinical studies based on more than 500 paediatric patients (from birth to 17 years) do not indicate that the safety profile of linezolid for paediatric patients differs from that for adult patients.

4.9 Overdose

No specific antidote is known.

No cases of overdose have been reported. However, the following information may prove useful:

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 haemoperfusion. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

Signs of toxicity in rats following doses of 3000 mg/kg/day linezolid were decreased activity and ataxia whilst dogs treated with 2000 mg/kg/day experienced vomiting and tremors.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 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.

5.2 Pharmacodynamic Properties

Pharmacotherapeutic group: Other antibacterials, ATC code: J 01 X 08.

General properties

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 ≤ 4mg/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.

Information from clinical trials

Studies in the paediatric population:

In an open study, the efficacy of linezolid (10 mg/kg q8h) was compared to vancomycin (10-15mg/kg q6- 24h) in treating infections due to suspected or proven resistant gram-positive pathogens (including nosocomial pneumonia, complicated skin and skin structure infections,

catheter related bacteraemia, bacteraemia of unknown source, and other infections), in children from birth to 11 years. Clinical cure rates in the clinically evaluable population were 89.3% (134/150) and 84.5%(60/71) for linezolid and vancomycin, respectively (95%CI: -4.9, 14.6).

5.3 Pharmacokinetic Properties

LINOX IV primarily contains (s)-linezolid which is biologically active and is metabolised to form inactive derivatives.

Absorption

Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing. Absolute oral bioavailability of linezolid (oral and intravenous dosing in a crossover study) is complete (approximately 100%). Absorption is not significantly affected by food and absorption from the oral suspension is similar to that achieved with the film-coated tablets.

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.

In another study following oral dosing of 600 mg twice daily to steady-state, Cmax and Cmin were determined to be 21.2 [5.8] mg/l and 6.15 [2.94] mg/l, respectively. Steady-state conditions are achieved by the second day of dosing.

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.

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.

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.

The clinical significance of these observations has not been established as limited safety data are currently available.

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.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those in humans. In sexually mature animals these effects were reversible. However, these effects did not reverse in juvenile animals treated with linezolid for nearly the entire period of sexual maturation. Abnormal sperm morphology in testis of adult male rats, and epithelial cell hypertrophy and hyperplasia in the epididymis were noted. Linezolid appeared to affect the maturation of rat spermatozoa. Supplementation of testosterone had no effect on linezolid-mediated fertility effects. Epididymal hypertrophy was not observed in dogs treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 times or equivalent, respectively, to those in humans. The same linezolid concentrations caused maternal toxicity in mice and were related to increased embryo death including total litter loss, decreased fetal body weight and an exacerbation of the normal genetic predisposition to sternal variations in the strain of mice. In rats, slight maternal toxicity was noted at exposures lower than clinical exposures. Mild fetal toxicity, manifested as decreased fetal body weights, reduced ossification of sternebrae, reduced pup survival and mild maturational delays were noted. When mated, these same pups showed evidence of a reversible dose-related increase in pre-implantation loss with a corresponding decrease in fertility. In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) at low exposure levels 0.06 times compared to the expected human exposure based on AUCs. The species is known to be sensitive to the effects of antibiotics.

Linezolid and its metabolites are excreted into the milk of lactating rats and the concentrations observed were higher than those in maternal plasma.

Linezolid produced reversible myelosuppression in rats and dogs.

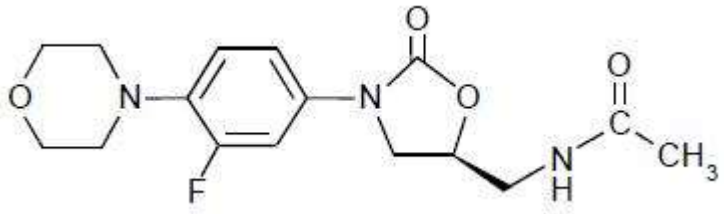
In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 of 3 male rats after 6 months of dosing, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The optic nerve degeneration observed was microscopically comparable to spontaneous unilateral optic nerve degeneration reported in aging rats and may be an exacerbation of common background change.

Preclinical data, based on conventional studies of repeated-dose toxicity and genotoxicity, revealed no special hazard for humans beyond those addressed in other sections of this Summary of Product Characteristics. Carcinogenicity / oncogenicity studies have not been conducted in view of the short duration of dosing and lack of genotoxicity.

7. DESCRIPTION

Linezolid injection contain linezolid, which is a synthetic antibacterial agent of the oxazolidinone class. The chemical name for linezolid is N-[[(5S)-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 337.4, and its chemical structure is represented below:



Linezolid injection is supplied as a ready-to-use sterile isotonic solution for intravenous infusion. Each mL contains 2 mg of linezolid. Linezolid injection is a clear, colourless solution to yellow coloured solution. **The** Excipients used **are** Dextrose (Anhydrous), Sodium citrate, Citric acid (Monohydrate), Sodium Hydroxide, Hydrochloric acid and Water for Injection.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Additives should not be introduced into this solution. If linezolid is to be given concomitantly with other drugs, each drug should be given separately in accordance with its own directions for use. Similarly, if the same intravenous line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following linezolid administration with a compatible infusion solution

Linox IV solution for infusion is known to be physically incompatible with the following compounds: amphotericin B, chlorpromazine hydrochloride, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and sulfamethoxazole / trimethoprim. Additionally, it is chemically incompatible with ceftriaxone sodium.

Special precautions for disposal and other handling

For single use only. Remove overwrap only when ready to use, then check for minute leaks by squeezing the bag firmly. If the bag leaks, do not use as sterility may be impaired. The solution should be visually inspected prior to use and only clear solutions, without particles should be used. Do not use these bags in series connections. Any unused solution must be discarded. No special requirements for disposal. Any unused medicinal product or waste material should be disposed of in accordance with local requirements. Do not reconnect partially used bags.

Linox IV solution for infusion is compatible with the following solutions: 5% glucose intravenous infusion, 0.9% sodium chloride intravenous infusion, Ringer-lactate solution for injection (Hartmann's solution for injection).

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

LINOX IV is available in 300 ml of plastic container.

8.4 Storage and Handing Instructions

Store at temperature not exceeding 30°C, protect from light. Do not freeze.

Keep out of reach of children

Linezolid I.V. Injection may exhibit a yellow colour that can intensify over time without adversely affecting potency.

The solution must be used immediately after the seal is first broken. If not use immediately, storage times & conditions are the responsibility of the user. Any unused solution must be discarded.

Do not use in series connection.

Do not introduce additives to this solution.

Do not reconnect partially used bottles.

Protect from light on removal from the manufacturer's original packing.

9. PATIENT COUNSELLING INFORMATION

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.

LINOX IV 600 mg

Linezolid

- Keep this leaflet. You may need to read it again.

- If you have any further questions, ask your doctor, pharmacist or nurse.

- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

What is in this leaflet?

1. What LINOX IV is and what it is used for

LINOX IV LINOX IV is an antibiotic of the oxazolidinones group that works by stopping the growth of certain bacteria (germs) that cause infections. It is used for the treatment of

Complicated/uncomplicated skin & skin structure infections/community acquired pneumonia

2. What you need to know before you use LINOX IV

Do not use LINOX IV

- If you are allergic to LINOX IV or any of the other ingredients of this medicine

- If you are taking or have taken within the last 2 weeks any medicines known as monoamine oxidase inhibitors (MAOIs for example phenelzine, isocarboxazid, selegiline, moclobemide). These medications may be used to treat depression or Parkinson's disease;

- If you are breast-feeding. This is because LINOX IV passes into breast milk and could affect the baby.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using LINOX IV.

LINOX IV may not be suitable for you if you answer **yes** to any of the following questions. In this case tell your doctor as he/she will need to check your general health and your blood pressure before and during your treatment or may decide that another treatment is better for you.

Ask your doctor if you are not sure whether these categories apply to you.

- Do you have high blood pressure, whether or not you are taking medicines for this?

- Have you been diagnosed with an overactive thyroid?

- Do you have a tumour of the adrenal glands (phaeochromocytoma) or carcinoid syndrome (caused by tumours of the hormone system with symptoms of diarrhoea, flushing of the skin, wheezing)?

- Do you suffer from manic depression, schizoaffective disorder, mental confusion or other mental problems?

Take special care with LINOX IV

Tell your doctor before you take this medicine if you:

- bruise and bleed easily

- are anaemic (have low red blood cells)

- are prone to getting infections

- have a history of seizures

- have liver problems or kidney problems particularly if you are on dialysis

- have diarrhoea

Tell your doctor immediately if during treatment you suffer from

- Problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.

- Loss of sensitivity in your arms or legs or a sensation of tingling or pricking in your arms or legs.

- You may develop diarrhoea while taking or after taking antibiotics, including LINOX IV. If this becomes severe or persistent or you notice that your stool contains blood or mucus, you should stop taking LINOX IV immediately and consult your doctor. In this situation, you should not take medicines that stop or slow bowel movement.

- Recurrent nausea or vomiting, abdominal pain or rapid breathing

Other medicines and LINOX IV

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

There is a risk that LINOX IV may sometimes interact with certain other medicines to cause side effects such as changes in blood pressure, temperature or heart rate.

Tell your doctor if you are taking or have taken within the last 2 weeks the following medicines as LINOX IV **must not** be taken if you are already taking these medicines or have taken them recently.

- Monoamine oxidase inhibitors (MAOIs for example phenelzine, isocarboxazid, selegiline, moclobemide). These may be used to treat depression or Parkinson's disease

Also tell your doctor if you are taking the following medicines. Your doctor may still decide to give you LINOX IV, but will need to check your general health and your blood pressure before and during your treatment. In other cases, your doctor may decide that another treatment is better for you.

- Decongestant cold or flu remedies containing pseudoephedrine or phenylpropanolamine.

- Some medicines used to treat asthma such as salbutamol, terbutaline, fenoterol.

- Certain antidepressants known as tricyclics or SSRIs (selective serotonin reuptake inhibitors). There are many of these, including amitriptyline, citalopram, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, sertraline.

- Medicines used to treat migraine such as sumatriptan and zolmitriptan.

- Medicines used to treat sudden, severe allergic reactions such as adrenaline (epinephrine).

- Medicines which increase your blood pressure, such as noradrenaline (norepinephrine), dopamine and dobutamine

- Medicines used to treat moderate to severe pain, such as pethidine.

- Medicines used to treat anxiety disorders, such as buspirone.

- Medicines that stop blood clotting, such as warfarin.

- An antibiotic called rifampicin.

LINOX IV with food and drink

- You can use LINOX IV either before, during or after a meal.

- Avoid eating large amounts of mature cheese, yeast extracts, or soya bean extracts e.g. soy sauce and drinking alcohol, especially draught beers and wine. This is because this medicine may react

With a substance called tyramine which is naturally present in some foods. This interaction may cause an increase in your blood pressure.

- If you develop a throbbing headache after eating or drinking, tell your doctor or pharmacist immediately.

Pregnancy, breast-feeding and fertility

The effect of LINOX IV in pregnant women is not known. Therefore, it should not be used in pregnancy unless advised by your doctor. If you are pregnant, think you may be pregnant or

are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

You should not breast-feed when using LINOX IV because it passes into breast milk and could affect the baby.

Driving and using machines

LINOX IV may make you feel dizzy or experience problems with your vision. If this happens, do not drive or operate any machinery. Remember that if you are unwell your ability to drive or operate machinery may be affected.

3. How to use LINOX IV

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Adults

This medicine will be given to you through a drip (by infusion into a vein) by a doctor or healthcare professional. The recommended dose for adults (18 years and older) is 300 ml (600 mg LINOX IV) twice daily which is given directly into the blood stream (intravenously) by a drip over a period of 30 to 120 minutes.

If you are on kidney dialysis, you should be given LINOX IV after your dialysis treatment.

A course of treatment usually lasts 10 to 14 days, but can last up to 28 days. The safety and effectiveness of this medicine have not been established for treatment periods longer than 28 days. Your doctor will decide how long you should be treated.

While you are using LINOX IV, your doctor should perform regular blood tests to monitor your blood count.

Your doctor should monitor your eyesight if you use LINOX IV for more than 28 days.

Use in children and adolescents

LINOX IV is not normally used to treat children and adolescents (under 18 years old).

If you use more LINOX IV than you should

If you are concerned that you may have been given too much LINOX IV, tell your doctor or a nurse at once.

If you forget to use LINOX IV

As you will be given this medicine under close supervision, it is very unlikely that you will miss a dose. If you think that you have missed a dose of treatment, tell a doctor or nurse at once. Do not take a double dose to make up for a forgotten dose.

4. Possible side effects

Like all medicines this medicine can cause side-effects, although not everybody gets them.

Tell your doctor, nurse or pharmacist immediately if you notice any of these side effects during your treatment with LINOX IV.

The serious side effects (with frequency in brackets) of LINOX IV are

- Severe skin disorder (not known), swelling, particularly around the face and neck (not known), wheezing and/or difficulty breathing (not known). This may be the sign of an allergic

reaction and it may be necessary for you to stop taking LINOX IV. Skin reactions such as red sore skin and flaking (dermatitis) (uncommon), rash (common), itching (common).

- Problems with your vision such as blurred vision (uncommon), changes in colour vision (not known), and difficulty in seeing detail (not known) or if your field of vision becomes restricted (rare).

- Severe diarrhoea containing blood and/or mucus (antibiotic associated colitis including pseudomembranous colitis), which in rare circumstances may develop into complications that are life-threatening (rare).

- Recurrent nausea or vomiting, abdominal pain or rapid breathing (not known).

- Fits or seizures (uncommon) have been reported with LINOX IV. You should let your doctor know if you experience agitation, confusion, delirium, rigidity, tremor, incoordination and seizure while also taking antidepressants known as SSRI's (not known).

- unexplained bleeding or bruising, which may be due to changes in the numbers of certain cells in the blood which may affect blood clotting or lead to anaemia (common).

- Changes in numbers of certain cells in the blood which may affect your ability to fight infection (common). Some signs of infection include: any fever (common), sore throat (uncommon), mouth ulcers (uncommon) and tiredness (uncommon).

- Inflammation of the pancreas (uncommon).

- Convulsions (uncommon).

- transient ischaemic attacks (temporary disturbance of blood flow to the brain causing short term symptoms such as loss of vision, leg and arm weakness, slurring of speech and loss of consciousness) (uncommon).

- "ringing" in the ears (tinnitus) (uncommon).

Numbness, tingling or blurred vision have been reported by patients who have been given LINOX IV for more than 28 days. If you experience difficulties with your vision you should consult your doctor as soon as possible.

Other side effects include:

Common (may affect up to 1 in 10 people)

- Fungal infections especially vaginal or oral "thrush"

- Headache

- Metallic taste in the mouth

- Diarrhoea, nausea or vomiting

- Changes in some blood test results including those measuring your kidney or liver function or blood sugar levels

- Difficulty in sleeping

- Increased blood pressure

- Anemias (low red blood cells)

- Dizziness

- Localised or general abdominal pain

- Constipation

- Indigestion
- Localised pain

Uncommon (may affect up to 1 in 100 people)

- Inflammation of the vagina or genital area in women
- Sensations such as tingling or feeling numb
- Swollen, sore, or discoloured tongue
- Pain at and around the place where the infusion (drip) was given
- Inflammation of the veins (including where the infusion (drip) was given)
- A need to urinate more often
- Chills
- Feeling thirsty
- Increased sweating
- Changes in proteins, salts or enzymes in the blood which measure kidney or liver function
- Hyponatraemia (low blood sodium levels)
- Kidney failure
- Reduction in platelets
- Abdominal bloating
- Injection site pain
- Increase in creatinine
- Stomach pain
- Changes in heart rate (e.g., increase rate)

Rare (may affect up to 1 in 1000 people)

- Superficial tooth discolouration, removable with professional dental cleaning (manual descaling)

Not known (frequency cannot be estimated from the available data)

- Alopecia (hair loss)
- Decrease of the blood cell count
- Weakness and/or sensory changes

5. How to store LINOX IV

As you will be given this medicine under close medical supervision, Hospital Staff will comply with the following advices:

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bag after EXP. The first two digits indicate the month and the last four digits indicate the year. The expiry date refers to the last day of that month. Use the medicine as soon as the seal is broken.

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

Store in the original package (overwrap and carton) in order to protect from light.

Do not use this medicine if you notice that the solution is not clear and contains particles.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines that you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What LINOX IV contains

-The active substance is Linezolid. Each ml of solution contains 2 mg Linezolid.

-The other ingredients are Dextrose (Anhydrous), Sodium citrate, Citric acid (Monohydrate), Sodium Hydroxide, Hydrochloric acid and Water for Injection.

What LINOX IV looks like and contents of the pack

LINOX IV injection is a clear, colourless solution to yellow coloured solution

LINOX IV is available in 300 ml of plastic container.

10. DETAILS OF MANUFACTURER

Manufactured in India by:

Axa Parentrals Ltd.

Plot No. 936, 937 & 939,

Village – Kishanpur,

Jamalpur, Roorkee- 247667, (Uttarakhand).

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg. Lic. No. : 15/UA/SC/P (LVP)/2007 issued on 18.05.2017

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

Indrad – 382721, Dist. Mehsana, India.

IN/ LINOX IV 600 mg/Apr -20/01/PI