SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MULTIFLEX LINEZOSEL 2 mg/ml I.V. Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION Active ingredient:

Linezolid 2 mg/ml

Excipients:

Dextrose Monohydrate (glucose)	50.24 mg/ml
Sodium citrate dihydrate	1.64 mg/ml
Sodium hydroxide	for pH 4.8 q.s.

"For the list of excipients, see section 6.1."

3. PHARMACEUTICAL FORM

Solution for infusion.
Isotonic, clear, pale yellow solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

MULTIFLEX LINEZOSEL formulations are indicated in the treatment of the following infections caused by susceptible strains of the designated microorganisms. MULTIFLEX LINEZOSEL is not active against infections caused by Gram negative pathogens. Specific therapy against Gram negative organisms must be initiated concomitantly if a Gram negative pathogen is documented or suspected.

- **Vancomycin-resistant *Enterococcus faecium* infections:** Including those associated 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 (diabetic foot infections without concurent osteomyelitis): caused by *Staphylococcus aureus* (methicillin susceptible and-resistant strains), *Streptococcus pyogenes,* or *Streptococcus agalactiae*. MULTIFLEX LINEZOSEL is indicated in adults for the treatment of complicated skin and soft tissue infections **only** when microbiological testing

has established that the infection is known to be caused by susceptible Gram positive bacteria. MULTIFLEX LINEZOSEL is not active against infections caused by Gram negative pathogens. MULTIFLEX LİNEZOSEL, Linezolid should only be used in patients with complicated skin and soft tissue infections 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. The use of MULTIFLEX LINEZOSEL in decubitus ulcers has not been studied

- **Uncomplicated skin and skin structure infections:** Caused by *Staphylococcus aureus* (meticillin 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).

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

4.2. Posology and method of administration

Posology/Frequency and duration of administration:

Adults:

Suggested dosages of MULTIFLEX LINEZOSEL for treatment of indications are given in the table below. MULTIFLEX LİNEZOSEL doses are given every 12 hours. Adult patients who have methicil in resistant *Staphylococcus aureus* infection should be treated with MULTIFLEX LINEZOSEL 600 mg every 12 hours.

Dosage Guidelines for MULTIFLEX LINEZOSEL			
	Dosages and Route of Administration		**Sugge sted duration of Tre atment**
Infection*	**Pe diatric Patie nts (Birth through 11 Years of Age)****	**Adults and Adole scents (12 to 18 of age)**	
Vancomycin-resistant *Enterococcus faecium* infections, including concurrent bacteremia	10 mg/kg IV or oral q8h +	600 mg IV or oral q12h +	14 to 28 days
Nosocomial pneumonia Complicated skin and skin structure infections Community-acquired pneumonia, including concurrent bacteremia	10 mg/kg IV or oral q8h +	600 mg IV or oral q12h +	10 to 14 days
Uncomplicated skin and skin structure infections	<5 yrs: 10 mg/kg oral q8h + 5-11 yrs: 10 mg/kg oral+ q12h	Adults: 400 mg oral q12h + Adolescents: 600 mg oral q12h +	10 to 14 days
* Due to the designated pathogens (See Section 4.1. Therapeutic indications)			
+ Oral dosing using linezolid tablets			
** Neonates <7 days: Pre-term neonates < 7 days of age (gestational age < 34 weeks) 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			

In controlloed clinical trials, the protocol-defined duration of treatment for all infections ranged from 7 to 28 days. 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. Patients whose therapy is started with MULTIFLEX LINEZOSEL solution for infusion may be switched to either linezolid or oral suspension at the discretion of the physician, when clinically indicated.

Method of administration:

For intravenous use.

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

Additional information on special populations
Renal insufficiency:

No dose adjustment is required. (See 5.2 Pharmacokinetic properties and 4.4 Special warnings and precautions for use).

Patients with severe renal insufficiency (creatinine clearence < 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 MULTIFLEX LINEZOSEL 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 MULTIFLEX LINEZOSEL dose is removed during 3 hours of haemodi alysis, MULTIFLEX LINEZOSEL should be given after dialysis in patients receiving such treatment. The primary metabolites of MULTIFLEX LINEZOSEL 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, MULTIFLEX LINEZOSEL 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 MULTIFLEX LINEZOSEL administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure.

Hepatic insufficiency: 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. (See 5.2. Pharmacokinetic properties; 4.4 Special warnings and precautions for use).

Pediatric populations:
MULTIFLEX LİNEZOSEL dose is adjusted depending on age and weight in pediatric patients (See section 4.2 Posology and method of administration, Dosage Guidelines for MULTIFLEX LINEZOSEL).

Geriatric Populations**:**

There is no need for dose adjustment. (See 5.2. Pharmacokinetic properties; 4.4 Special warnings and precautions for use)

Other:

Dose adjustment by gender does not appear to be necessary.

4.3. Contraindications

MULTIFLEX LİNEZOSEL formulations are contraindicated in people who are hypersensitive to linezolid or to any of the excipients.

Monoamine Oxidase Inhibitors:

MULTIFLEX LINEZOSEL 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.

Potential interactions producing elevation of blood pressure

Unless blood pressure is monitored, MULTIFLEX LINEZOSEL should not be administered to patients with uncontrolled hypertension, phaeochromocytoma, thyrotoxicosis and/or taking following medications: Directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine, phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), agents (e.g. dopamine, dobutamine) (see 4.5 Interaction with other medicinal products and other forms of interaction).

Potential Serotonergic Interactions:

Serotonin syndrome can occur with the co-administration of MULTIFLEX LINEZOSEL and serotonergic agents. 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 4.5 Interaction with other medicinal products and other forms of interaction), where patients can't be carefully observed for signs and/or symptoms of serotonin syndrome.

In case of life threatening infections in patients using a seratonergic agent after linezolid treatment has started, discontinuation of the agent should be followed by an expert.

MULTIFLEX LINEZOSEL should not be used in patients with bipolar depression, schizoaffective disorder and acute confusional situations.

Animal data suggest that MULTIFLEX LINEZOSEL and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration.

4.4. Special warnings and precautions for use

Transient myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving MULTIFLEX LINEZOSEL. In cases where the outcome is known, when MULTIFLEX LINEZOSEL 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. It is recommended that complete blood counts should be monitored weekly in patients who receive MULTIFLEX LINEZOSEL, especially longer than two weeks, with myelosuppression history, who are taking medications that can cause myelosupression concomitantly, who are taking or have previously taken antibiotic therapy for chronic infection. If significant myelosuppression occurs or increases severity during linezolid therapy, discontinuing the MULTIFLEX LINEZOSEL treatment should be considered.

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 fuly or partially recovered following discontinuation of linezolid with or without treatment for their anaemia.

Excess mortality was seen in patients treated with linezolid, relative to vancomycin/ dicloxacillin/ oxacillin, in an open-label study in seriously 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 (see section 4.1 Therapeutic indications). In these circumstances treatment against Gram negative organisms must be initiated concomitantly.
Linezolid is not active against infections caused by Gram negative pathogens. Specific therapy against Gram negative organisms must be initiated concomitantly if a Gram negative pathogen is documented or suspected. (See Section 4.1 Therapeutic indications)

Pseudomembranous colitis has been reported with nearly all antibacterial agents including linezolid. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent. In cases of suspected or verified antibiotic-associated colitis,discontinuation of linezolid may be warranted.Appropriate management measures should be instituted.
Pseudomembranous colitis, that's severity may range from mild to life threatening has been reported with nearly all antibacterial agents, including linezolid. Therefore, it is important toconsider this diagnosis in patients who present with diarrhoea subsequent to the administration of any antibacterial agent. In cases of suspected or verified antibiotic-associated colitis, discontinuation of linezolid may be warranted. Appropriate management measures should be instituted. Drugs inhibiting peristalsis are contraindicated in this situation.

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. 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 antibiotic-associated diarrhoea or antibiotic-associated colitis is suspected or confirmed, ongoing treatment with antibacterial agents should be discontinued.

When CDAD is diagnosed adequate therapeutic measures should be initiated immediately. Mild cases of CDAD usually respond to only discontinuation of the drug. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated in cases that range from moderate to serious.

Postmarketing cases of symptomatic hypoglycemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycemic agents when treated with linezolid, a reversible, nonselective MAO inhibitor. Some MAO inhibitors have been associated with hypoglycemic episodes in diabetic patients receiving insulin or hypoglycemic agents. While a causal relationship between linezolid and hypoglycemia has not been established, diabetic patients should be cautioned of potential hypoglycemic reactions when treated with linezolid. If hypoglycemia occurs, a decrease in the dose of insulin or oral hypoglycemic agent, or discontinuation of oral hypoglycemic agent, insulin, or linezolid may be required.

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.

Peripheral neuropathy, as well optic neuropathy and optic neuritis sometimes progressing to loss of vision, have been reported in patients treated with MULTIFLEX LINEZOSEL; these reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days.

If peripheral or optic neuropathy occurs, the continued use of MULTIFLEX LINEZOSEL should be weighed against the potential risks.

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. Visual function should be monitored in all patients taking MULTIFLEX LINEZOSEL for extended periods (≥ 3 months) and in all patients reporting new visual symptoms regardless of length of therapy.

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.

Lactic acidosis has been reported with the use of MULTIFLEX LINEZOSEL. 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 MULTIFLEX LINEZOSEL should receive immediate medical evaluation. 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.

Convulsions have been reported to occur in patients when treated with Zyvox. 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.

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 (See Sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction)

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.
Co-Administration of rifampicin with linezolid in health volunteers result in a 21% decrease in linezolid Cmax and a 32% decrease in linezolid AUC 0-12. The mechanism of this interaction is not fully understood.

Patients receiving linezolid should be warned about the need to avoid consuming large amounts of foods or beverages with hight yramine content (See 4.5 Interaction with other medicinal products and other forms of interaction).

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

The use of antibiotics may occasionally resul 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.

MULTIFLEX LİNEZOSEL should not be used in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid, thyrotoxicosis, bipolar depression, schizoaffective disorder, acute confusional states. (See Section 4.3)

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 (see sectionsm4.2 and 5.2 Posology and method of administration and Pharmacokinetic properties).

It is recommended that linezolid should be given to patients with severe hepatic insufficiency only when the perceived benefit outweighs the theoretical risk (see sections 4.2 and 5.2 Posology and method of administration and Pharmacokinetic properties).

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 (See Section 5.3 Preclinical safety data).

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.

Each ml of solution also contains 0.38 mg sodium. The sodium content should be taken into account in patients on a controlled sodium diet.

Each ml of the solution contains 50.24 mg/ml glucose. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance.

4.5. Interaction with other medicinal products and other forms of interaction

In normotensive healthy volunteers, MULTIFLEX LINEZOSEL enhanced the increases in blood pressure caused by pseudoephedrine and phenylpropanolamine hydrochloride. Co- administration of MULTIFLEX LINEZOSEL with either pseudoe phedrine 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 seratonergic 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, 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 (see section 4.3 Contraindications), management of patients for whom treatment with linezolid and serotonergic agents is essential, is described in section 4.4 Special warnings and precautions for use**.**

Drugs metabolised by cytochrome P450

MULTIFLEX LINEZOSEL does not metabolize to a detectable amount with the human cytochrome P450 system and does not inhibit the activities of clinically important CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, the interaction of MULTIFLEX LINEZOSEL with CYP450 -

induced drugs is not expected.

Antibiotics

Rifampicin: The effect of rifampicin on the pharmacokinetics of linezolid was studied in 16 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.

Aztreonam

The pharmacokinetics of MULTIFLEX LINEZOSEL and astreonam does not change when administered concomitantly.

Gentamicin

The pharmacokinetics of MULTIFLEX LINEZOSEL and gentamicin does not change when administered concomitantly.

Monoamine oxidase inhibitors

MULTIFLEX LINEZOSEL is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). That's why linezolid has the potential for interaction with adrenergic and serotonergic agents. 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.

Adrenergic agents

Some individuals receiving MULTIFLEX LINEZOSEL may experience areversible 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.

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).

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.

Risk of seizure increases when MULTIFLEX LİNEZOSEL is concomitantly used with tramadol.

Risk of myelosupression increaseswhen used concomitantly with other myelosupressant medication.

Drug-Laboratory Test Interactions

There are no reported drug-laboratory test interactions.

Additional information about special populations

Renal/Hepatic insufficiency: There are no interaction studies detected.

Pediatric population:

There are no interaction studies detected.

4.6. Pregnancy and lactation General advice

Pregnancy Category: C

Women of childbearing potential / Birth control (Contraception)

An effective way of birth control should be used during treatment.

Pregnancy

There are no adequate and well controlled studies in pregnant women. LINEZOSEL should only be used during pregnancy if the potential benefit outweighs the theoretical risk.

Teratogenic effects were not proved in reproduction ability studies on mice and rats treated by MULTIFLEX LINEZOSEL. In rats, mild fetal toxicity was observed at maternal toxic dose level. In rats, mild fetal toxicity was observed as decreased fetal body weights and reduced ossification of sternebrae, a finding often seen in association with decreased fetal body weights. This situation causes survival of pups to be decreased and delayed their maturing. Male and female pups permitted to mature to reproductive age, when mated, showed an increase in preimplantation loss.

There are no adequate data from the use of linezolid in pregnant women Studies in animals

have shown reproductive toxicity (see section 5.3 Preclinical safety data). A potential risk for humans exists.

Lactation

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.

Reproductive ability/fertility

MULTIFLEX LINEZOSEL decreases fertility in male rats. The possible effect of it on reproduction system on males is unknown. (See section 5.3)

4.7. Effects on ability to drive and use machines

The effect of MULTIFLEX LİNEZOSEL on ability to drive and use machines is not evaluated. Patients should be warned about the potential for dizziness or symptoms of visual impairment (as described in section 4.4 Special warnings and precautions for use and 4.8. Undesirable effects) whilst receiving MULTIFLEX LINEZOSEL and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8. Undesirable effects

Undesirable effects are listed in following categories:

The information 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 recommende MULTIFLEX LINEZOSEL doses for up to 28 days.

Most common adverse reactions were reported as; headache (6.5%), diarrhea (8.4%), nausea (6.3%) and vomiting (4%).

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.

Undesirable effects are listed in following categories:

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)

Infectations and infestations

Common : Candidias (especially oral and vaginal candidiasis) or fungal infections, moniliasis
Uncommon : Vaginitis
Not known : Antibiotic-associated colitis (including pseudomembranous colitis)

Blood and lymphatic system disorders

Common : Anemia*
Uncommon : Eozinofili Leucopenia * neutropenia thrombocytopenia
Rare : Pancytopenia *
Not known : Myelosuppresion*, sideroblastic anaemia*

Immune system disorders

Not known : Anaphylaxis

Metabolism and nutrition disorders

Uncommon : Hiponatraemia
Not known : Lactic acidosis*

Psychiatric disorders

Common : Insomnia

Nervous system disorders

Common : Headache, taste perversion (metallic taste), drowsiness
Uncommon : Convulsion, hipoaesthesia, paraesthesia
Not known : Seratonin syndrome**, peripheral neuropathy*

Eye Disorders

Uncoman : Blurred Vision*
Rare : Hemianosia*
Not Known : Optic neuropathy*, optic neuritis*, visual loss*, visual acuity decrease*, color changes in vision*

Ear and labyrinth disorders

Uncommon : Tinnitus

Cardiac disorders

Rare : Arrhythmia (tachycardia)

Vascular disorders

Uncommon : Hypertension

Rare : Transient ischaemic attacks, phlebitis/thrombophlebitis

Gastrointestinal disorders

Common : diarrhoea, nausea, vomiting, abdominal pain/cramps/distention constipation, dyspepsia

Uncommon : Pancreatitis gastritis, abdominal bloating dry mouth glossitis, loose stools, stomatitis, tongue discoloration or disorder.

Not known : Superficial tooth discoloration

Hepato-biliary disorders

Common : Abnormal liver function test, increased AST, ALT and alkaline phosphatase

Uncommon : Increased total bilirubin

Skin and subcutaneous tissue disorders

Common : Rash, pruritus

Uncommon : Dermatitis, diaphoresis, pruritus sweating, urticaria

Not known : Stevens-Johnson syndrome, toxic epidermal necrolysis Bullous disorders such as described, angioedema, alopecia

Renal and urinary disorders

Common : Increased BUN

Uncommon : Renal failure, polyuria, increased creatinine

Rare : Renal failure

Reproductive system and breast disorders

Uncommon : Vulvovajinal disorder

General disorders and administration site conditions

Common : Fever localised pain

Uncommon : Chills,fatigue,injection site pain,increased thirst

*In controlled clinical trials where MULTIFLEX LINEZOSEL was administered for up to 28 days, less than 2% 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. The following adverse reactions to MULTIFLEX LINEZOSEL were considered to be serious in rare cases: localised abdominal pain, transient ischaemic attacks, hypertension.

Investivations Biochemistry:

Common : Increased BUN, LDH, creatine kinase, lipase, amylase or non fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate

Uncommon: Increased sodium or calcium. Decreased non fasting glucose. Incresaed or decreased chloride

Haematology

Common : Increased neutrophils or eosinophil. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.

Uncommon: Increased reticulocyte count. Decreased neutrophils.

* see section 4.4

* See section 4.3 and 4.5

+In controlled clinical trials where MULTIFLEX LINEZOSEL was administered for up to 28 days, less than 0.1% 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.

The following adverse reactions to MULTIFLEX LINEZOSEL were considered to be serious in rare cases: localised abdominal pain,transient ischaemic attacks,hypertension,pancreatitis and kidney disorder.

In clinical trials there was only one drug related(tachycardia) was reported.

Additional information regarding special populations

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.

Postmarketing Experience

Blood and Iymphatic system disorders: Anemia, l eukopenia, neutropenia, thrombocytopenia, pancytopenia , myelosuppression, sideroblastic anaemia(see section 4.4 Special warnings and precautions for use).Cases of anemia requiring blood transfusion have also been reported post marketing with more cases occuring in patients who received MULTIFLEX LINEZOSEL therapy for more than 28 days. Immune system disorders: Anaphylaxis. Metabolism and nutrition disorders: Hypoglycemia, lactic acidosis (See section 4.4 Special warnings and precautions for use). Nervous system disorders: Peripheral neuropathy, convulsions, serotonin syndrome (See section 4.4 Special warnings and precautions for use) Peripheral neuropathy have been reported in patients treated for longer than the maximum recommended duration of 28 days.

Convulsion have been reported to occur in patients when treated with MULTIFLEX LINEZOSEL. 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 seizures.

Causes of seratonin syndrom has been reported.

Eye disorder:Optic neuropathy which can sometimes progres to loss of vision have been reported in patients treated with MULTOFLEX LINEZOSEL,primarily those patiens treated for longer than the maximum recommended duration 28 days.See section 4.4 Special warnings and precautions for use) Skin ans subcutaneous tissue disorders :Anaphylaxi,angioedema, and bulluous skin disorders such as those described as Steens Johnsons's syndrome toxic epidermal necrolysis,angioedema,alopecia have been reported.

Gastroinstestinal disorders: Tongue discoloration and very rare superficial tooth discolaration have been reported with use of linezolid. The tooth discoloration was removable wtih professional dental cleaning (manual descaling)

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9. Overdose and treatment

No specific antidote is known.

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. Pharmacodynamic properties

Pharmacotherapeutic group: Other antibacterials
ATC code : J01XX08

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.

The invitro 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.

Susceptibility

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.

Linezosel has been found effective in many of following microorganisms in both *in vivo* and

in vitro:

Susceptible Gram Positive Aerobes:

*Enterococcus faecium**

Enterococcus faecalis

*Staphylococcus aureus**

Coagulase negative staphylococci

*Streptococcus agalactiae**

*Streptococcus pneumoniae**

*Streptococcus pyogenes**

Group C streptococci

Group G streptococci

Susceptible Gram Positive Anaerobes:

Clostridium perfringens

Peptostreptococcus anaerobius

Peptostreptococcus species

Resistant organisms

Haemophilus influenzae

Moraxella catarrhalis

Neisseria species

Enterobactericeae

Pseudomonas species

* Clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications

Whereas linezolid shows some in vitro activity against Legionel a, 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 methicil in-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.

Studies in the paediatric population
In an open study, the efficacy of linezolid (10 mg/kg q8h) was compared to vancomycin (10-15mg/kg 6- 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).

5.2. Pharmacokinetic properties

MULTIFLEX LINEZOSEL 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 1-2 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 teady-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.
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 expos ure measured as AUC0-(∞) values is similar under both conditions.

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 dossing.
Animal and human pharmacokinetic studies have demonstrated that linezolid readily distributes to well - perfused tissues.

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

Non-renal clearance accounts for approximately 65% of the total clearance of linezolid. A smal 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.

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%). Virtual y 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.

Linearity/non-linearity

A smal 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.

The mean pharmacokinetic parameters of linezolid in adults after single and multiple oral and intravenous (IV) doses are summarized in table below.

Mean (Standard Deviation) Pharmacokinetic Parameters of Line zolid in Adults						
Dose of linezolid	**Cmax µg/mL**	**Cmin µg/mL**	**Tmax hour**	**AUC* µg hour/mL**	**t1/2 hour**	**CL Ml/min**
600 mg tablet						
Single dose	12.70 (3.96)	--	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
Every 12 hours	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg IV infusion solution+						
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)
600 mg oral suspension						
Single dose	11.00 (2.76)	--	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)
*AUC for single dose=AUC0-(∞); for multiple dose=AUC0-[tgr]						
+ Data dose-normalized from 625 mg, IV dose was given as 0.5-hour infusion.						
Cmax = Maximum plasma concentration; Cmin = Minimum plasma concentration; ; Cmin = Minimum plasma concentration; Tmax = Time to Cmax; Area under concentration-time curve; t1/2 = Elimination half-life; CL = Systemic clearance						

Characteristics of patients

Elderly patients:

The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 and over.

Paediatric patients:

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 600 mg 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 fol owing 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.

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 halflife 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.

Renal insufficiency

After single doses of 600 mg, there was a 7-8fold 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 10fold 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 insufficiency:

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.

On the basis of available information, no dose adjustment is recommended for patients with hepatic insufficiency.

5.3. Preclinical safety data

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those expected 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 expected 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 expected 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 microscopiallay 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 in the standard battery of studies.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium citrate dihydrate,
Citric acid anhydrous,
Dextrose monohydrate (glucose),
Sodium hydroxide,
Hydrochloric acid,
Water for injection

6.2. Incompatibilities

In particular, physical incompatibilities resulted when MULTIFLEX LINEZOSEL intravenous infusion solution 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 MULTIFLEX LINEZOSEL intravenous infusion solution 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 MULTIFLEX LINEZOSEL injection with an infusion solution compatible with MULTIFLEX LINEZOSEL injection and with any other drug(s) administered via this common line.

MULTIFLEX LINEZOSEL intravenous infusion solution is compatible with following solutions:
5% Dextrose Injection 0.9% Sodium Chloride Injection Lactated Ringer's Injection.

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store it in its aluminum foil packing until time of usage.

This product should be used right after bag is opened. Unused solution should be discarded.

Store at room temperature below 25ºC. Protect from freezing. MULTIFLEX LINEZOSEL may exhibit a yellow color that can intensify over time without adversely affecting potency

6.5. Nature and contents ofcontainer

Non-PVC (polyolefin) bag with two outputs with protective Al overpouch closed by heat, 300 ml (1 or 10 pieces)

6.6. Special precautions for disposal and otherhandling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

MULTIFLEX LINEZOSEL intravenous infusion solution 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. Keep the infusion bags in the overwrap until ready to use (See Special precautions for storage). MULTIFLEX LINEZOSEL should be administered by intravenous infusion over a period of 30 to 120 minutes.

Do not use this intravenous infusion bag in series connections. (See Incompatibilities section)

Additives should not be introduced into this intravenous solution. If linezolid 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.

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S)

2015/81

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