TEDIZ®
(Tedizolid Phosphate)

1. NAME OF THE PRODUCT

TEDIZ® (Tedizolid Phosphate) 200mg Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TEDIZ® 200mg Injection

Each vial contains:

Tedizolid Phosphate MS.....200mg

3. PHARMACEUTICAL FORM

Powder for solution for infusion

Appearance: White to off-white colored, lyophilized cake or powder free from foreign particles.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS:

Acute Bacterial Skin and Skin Structure Infections: TEDIZ® is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes, Streptococcus agalactiae, Streptococcus anginosus* Group (including *Streptococcus anginosus, Streptococcus intermedius,* and *Streptococcus constellatus),* and *Enterococcus faecalis* in adults and paediatric patients (at least 26 weeks gestational age and weighing at least 1kg). Consideration should be given to official guidance on the appropriate use of antibacterial agents.

Usage to Reduce Development of Drug-Resistant Bacteria: To reduce the development of drug-resistant bacteria and maintain the effectiveness of Tedizolid Phosphate and other antibacterial drugs, TEDIZ® should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2. POSOLOGY AND METHOD OF ADMINISTRATION:

Posology:

TEDIZ® film-coated tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the

parenteral formulation may be switched to the oral presentation when clinically indicated.

Recommended dose and duration: The recommended dosage for adults and adolescents 12 years of age and older is 200mg once daily for 6 days with the infusion time of 1 hour. The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established

Missed dose: If a dose is missed it should be given to the patient as soon as possible anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remains before the next dose, then the physician should wait until the next scheduled dose. A double dose should not be given to compensate for a missed dose.

Elderly (≥ 65 years): No dosage adjustment is required. The clinical experience in patients ≥ 75 years is limited.

Hepatic impairment: No dosage adjustment is required.

Renal impairment: No dosage adjustment is required.

Recommended Dosage of Tedizolid Phosphate for Injection for Paediatric Patients:

Intravenous Dosage: The recommended intravenous dosage of TEDIZ® Injection for paediatric patients (at least 26 weeks gestational age and weighing at least 1kg).

Weight Band (kg)	Dose	Frequency	Infusion Time	Duration
Paediatric Patients Weighing Less than 2kg				
1 to less than 2*	3mg/kg	Twice daily	1 hour	6 days
Paediatric Patients Weighing at Least 2kg				
2 to less than 3	6mg	Twice daily	1 hour	6 days
3 to less than 6	12mg			
6 to less than 10	20mg			
10 to less than 14	30mg			
14 to less than 20	40mg			
20 to less than 35	60mg			
Paediatric Patients Weighing at Least 35kg				
Greater than or equal to 35	200mg	Once daily	1 hour	6 days

*Recommended Dosage for 1kg to less than 2kg is based on actual body weight.

Method of administration: Administer Tedizolid phosphate for injection as an intravenous infusion only. Do not administer as an intravenous push or bolus. Do not mix Tedizolid phosphate for Injection with other drugs when administering. It is not intended for intra-arterial, intramuscular, intrathecal,

intraperitoneal, or subcutaneous administration. The intravenous bag containing the reconstituted and diluted intravenous solution should be inspected visually for particulate matter prior to administration. Discard if visible particles are observed. The resulting solution is clear and colorless to pale-yellow in color. After reconstitution and dilution, Tedizolid phosphate for Injection is to be administered via intravenous infusion using a total time of 1 hour. The total time from reconstitution to the end of administration of Tedizolid phosphate for Injection should not exceed 24 hours at either room temperature or under refrigeration at 2°C to 8°C. Discard unused portion.

Preparation and Administration of Intravenous Solution: Tedizolid phosphate is supplied as a sterile, lyophilized powder for injection in single-dose vials of 200mg. Each 200mg vial must be reconstituted with Sterile Water for Injection and subsequently diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Tedizolid phosphate vials contain no antimicrobial preservatives and are intended for single dose only. Discard any unused portion.

Preparation of Tedizolid phosphate for Injection: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The contents of the vial should be reconstituted using aseptic technique as follows: Note: To minimize foaming, AVOID vigorous agitation or shaking of the vial during or after reconstitution.

For Adults and Paediatrics Patients Weighing at least 35kg:

1. Reconstitute the Tedizolid phosphate vial with 4mL of Sterile Water for Injection to provide a concentration of 50mg/mL in each vial.
2. Gently swirl the contents and let the vial stand until the cake has completely dissolved and any foam disperses. Inspect the vial to ensure the solution contains no particulate matter and no cake or powder remains attached to the sides of the vial. If necessary, invert the vial to dissolve any remaining powder and swirl gently to prevent foaming. The reconstituted solution is clear and colorless to pale-yellow in color; the total time from reconstitution to the end of administration should not exceed 24 hours at either room temperature or under refrigeration at 2°C to 8°C. Tilt the upright vial and insert a syringe with appropriately sized needle into the bottom corner of the vial and remove 4mL of the reconstituted solution for the 200 mg dose. Do not invert the vial during extraction.
3. The reconstituted solution must be further diluted in 250mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Slowly inject the required volume of reconstituted solution as determined in Step 2 into a 250mL bag of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Invert the bag gently to mix. Do NOT shake the bag as this may cause foaming.

For Paediatric Patients Weighing Less than 35kg:

1. Reconstitute the Tedizolid phosphate vial with 4mL of Sterile Water for Injection to provide a concentration of 50mg/mL in each vial.
2. Gently swirl the contents and let the vial stand until the cake has completely dissolved and any foam disperses.
3. Inspect the vial to ensure the solution contains no particulate matter and no cake or powder remains attached to the sides of the vial. If necessary, invert the vial to dissolve any remaining powder and swirl gently to prevent foaming. The reconstituted solution is clear and colorless to pale-yellow in color; the total time from reconstitution to the end of administration should not exceed 24 hours at either room temperature or under refrigeration at 2°C to 8°C. Prepare a stock solution (100mL of 0.8mg/mL tedizolid phosphate): Tilt the upright vial and insert a syringe with appropriately sized needle into the bottom corner of the vial and remove 1.6mL of the reconstituted solution and add it to an infusion bag containing 98.4mL of 0.9% Sodium Chloride Injection or 5% Dextrose Injection. Do not invert the vial during extraction.
4. Prepare the required volume of stock solution for infusion: Refer to Table to convert the dose in mg to the appropriate volume of stock solution to be administered. Transfer this volume of stock solution to an adequately sized infusion bag or infusion syringe. It may be necessary to round to the nearest graduation mark of an appropriately sized syringe for smaller volumes. The total time from reconstitution to the end of administration should not exceed 24 hours at either room temperature or under refrigeration at 2°C to 8°C.

Preparation of Tedizolid Phosphate for Injection for Paediatric Patients Weighing 1kg to Less than 35kg from the 100mL Stock Solution of 0.8 mg/mL Tedizolid Phosphate

Body Weight (kg)	**Amount of Tedizolid Phosphate per dose (given twice daily)**	**Volume of stock solution (0.8mg/mL) to be transferred to an adequately sized infusion bag or infusion syringe**
Paediatric Patients Weighing Less than 2kg		
1 to less than 2	3mg/kg	Volume (mL) = Weight (kg) x 3.75mL/kg
Paediatric Patients Weighing at Least 2kg		
2 to less than 3	6mg	7.5mL
3 to less than 6	12mg	15mL
6 to less than 10	20mg	25mL
10 to less than 14	30mg	37.5mL
14 to less than 20	40mg	50mL
20 to less than 35	60mg	75mL

4.3. CONTRAINDICATIONS:

Hypersensitivity to the active substance or to any of the excipients.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE:

Patients with neutropenia: The safety and efficacy of tedizolid phosphate in patients with neutropenia (neutrophil counts <1,000 cells/mm3) have not been investigated. In an animal model of infection, the antibacterial activity of tedizolid was reduced in the absence of granulocytes. The clinical relevance of this finding is unknown. Alternative therapies should be considered when treating patients with neutropenia and ABSSSI.

Mitochondrial dysfunction: Tedizolid inhibits mitochondrial protein synthesis. Adverse reactions such as lactic acidosis, anaemia and neuropathy (optic and peripheral) may occur as a result of this inhibition. These events have been observed with another member of the oxazolidinone class when administered over a duration exceeding that recommended for tedizolid phosphate.

Myelosuppression: Thrombocytopenia, decreased haemoglobin and decreased neutrophils have been observed during treatment with tedizolid phosphate. Anaemia, leucopenia and pancytopenia have been reported in patients treated with another member of the oxazolidinone class and the risk of these effects appeared to be related to the duration of treatment. Most cases of thrombocytopenia occurred with treatment lasting longer than the recommended duration. There may be an association with thrombocytopenia in patients with renal insufficiency. Patients who develop myelosuppression should be monitored and the benefit-risk should be re-evaluated. If treatment is continued, close monitoring of blood counts and appropriate management strategies should be implemented.

Peripheral neuropathy and optic nerve disorders: Peripheral neuropathy, as well as optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with another member of the oxazolidinone class with treatment durations exceeding that recommended for tedizolid phosphate. Neuropathy (optic and peripheral) has not been reported in patients treated with tedizolid phosphate at the recommended treatment duration of 6 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.

Lactic acidosis: Lactic acidosis has been reported with the use of another member of the oxazolidinone class. Lactic acidosis has not been reported in patients treated with tedizolid phosphate at the recommended treatment duration of 6 days.

Hypersensitivity reactions: Tedizolid phosphate should be administered with caution in patients known to be hypersensitive to other oxazolidinones since cross-hypersensitivity may occur.

***Clostridioides difficile* associated diarrhoea:** *Clostridioides difficile* associated diarrhoea (CDAD) has been reported for tedizolid phosphate. CDAD may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*. CDAD must be considered in all patients who present with severe diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, tedizolid phosphate and, if possible, other antibacterial agents not directed against *C. difficile* should be discontinued and adequate therapeutic measures should be initiated immediately. Appropriate supportive measures, antibiotic treatment of *C. difficile*, and surgical evaluation should be considered. Medicinal products inhibiting peristalsis are contraindicated in this situation.

Monoamine oxidase inhibition: Tedizolid is a reversible, non-selective inhibitor of monoamine oxidase (MAO) in vitro.

Serotonin syndrome: Spontaneous reports of serotonin syndrome associated with the co-administration of oxazolidinones, including tedizolid phosphate, together with serotonergic agents (such as antidepressants and opioids) have been reported. Caution should be exercised when tedizolid is used with these medicinal products. 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.

Non-susceptible microorganisms: Prescribing tedizolid phosphate in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria. Tedizolid is generally not active against Gram-negative bacteria.

Development of Drug-Resistant Bacteria: Prescribing Tedizolid phosphate in the absence of a proven or strongly suspected bacterial infection or prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Limitations of the clinical data: The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established. In ABSSSI, the types of infections treated were confined to cellulitis/erysipelas or major cutaneous abscesses, and wound infections only. Other types of skin infections have not been studied. There is limited experience with tedizolid phosphate in the treatment of patients with concomitant acute bacterial skin and skin structure infections and secondary bacteraemia and no experience in the treatment of ABSSSI with severe sepsis or septic shock. Controlled clinical studies did not include patients with neutropenia (neutrophil counts <1,000 cells/mm3) or severely immunocompromised patients.

Sodium: This medicinal product contains less than 1mmol sodium (23mg) per vial, that is to say essentially 'sodium-free'.

4.5. INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTIONS:

Pharmacokinetic interactions:

In a clinical study comparing the single dose (10mg) pharmacokinetics of rosuvastatin (Breast Cancer Resistant Protein [BCRP] substrate) alone or in combination with tedizolid phosphate (once-daily 200mg oral dose), rosuvastatin AUC and C_{max} increased by approximately 70% and 55%, respectively, when co-administered with tedizolid phosphate. Therefore, orally administered tedizolid phosphate can result in inhibition of BCRP at the intestinal level. If possible, an interruption of the co-administered BCRP substrate medicinal product (such as imatinib, lapatinib, methotrexate, pitavastatin, rosuvastatin, sulfasalazine, and topotecan) should be considered during the 6 days of treatment with oral tedizolid phosphate.

Pharmacodynamic interactions:

Monoamine oxidase inhibitors: Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) in vitro; however, no interaction is anticipated when comparing the IC_{50} for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies to determine effects of 200mg oral tedizolid phosphate at steady state on pseudoephedrine and tyramine pressor effects were conducted in healthy volunteers. No meaningful changes in blood pressure or heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity was observed.

Potential serotonergic interactions: The potential for serotonergic interactions has not been studied in either patients or healthy volunteers.

Post-marketing experience: there have been reports of patients experiencing serotonin syndrome while taking tedizolid and serotonergic agents (antidepressants, opioids) which resolved on discontinuation of one or both medications.

4.6. FERTILITY, PREGNANCY AND LACTATION:

Fertility: The effects of tedizolid phosphate on fertility in humans have not been studied. Animal studies with tedizolid phosphate do not indicate harmful effects with respect to fertility.

Pregnancy: There are no data from the use of tedizolid phosphate in pregnant women. Studies in mice and rats showed developmental effects. As a precautionary measure, it is preferable to avoid the use of tedizolid phosphate during pregnancy.

Breast-feeding: It is unknown whether tedizolid phosphate or its metabolites are excreted in human milk. Tedizolid is excreted in the breast milk of rats. A risk to the breast-feeding infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tedizolid

phosphate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Tedizolid Phosphate may have a minor influence on the ability to drive and use machines as it may cause dizziness, fatigue or, uncommonly, somnolence.

4.8. UNDESIRABLE EFFECTS:

The adverse reactions ranked under headings of system organ class and frequency using the following convention: 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).

Infections and infestations:

Uncommon: Vulvovaginal mycotic infection, fungal infection, vulvovaginal candidiasis, abscess, *Clostridioides difficile* colitis, dermatophytosis, oral candidiasis, respiratory tract infection.

Blood and lymphatic system disorders:

Uncommon: Lymphadenopathy.

Not known: Thrombocytopenia.

Immune system disorders:

Uncommon: Drug hypersensitivity.

Metabolism and nutrition disorders:

Uncommon: Dehydration, diabetes mellitus inadequate control, hyperkalaemia.

Psychiatric disorders:

Uncommon: Insomnia, sleep disorder, anxiety, nightmare.

Nervous system disorders:

Common: Headache, dizziness.

Uncommon: Somnolence, dysgeusia, tremor, paraesthesia, hypoaesthesia, VIIth nerve paralysis.

Eye disorders:

Uncommon: Vision blurred, vitreous floaters, visual impairment.

Vascular disorders:

Uncommon: Flushing, hot flush, hypertension.

Cardiac disorders:

Uncommon: Bradycardia, palpitations, tachycardia.

Respiratory, thoracic and mediastinal disorders:

Uncommon: Cough, nasal dryness, pulmonary congestion.

Gastrointestinal disorders:

Common: Nausea, diarrhoea, vomiting.

Uncommon: Abdominal pain, constipation, abdominal discomfort, dry mouth, dyspepsia, abdominal pain upper, flatulence, gastrooesophageal reflux disease, haematochezia, retching.

Skin and subcutaneous tissues disorders:
Common: Pruritus generalised.
Uncommon: Hyperhidrosis, pruritus, rash, urticaria, alopecia, rash erythematous, rash generalised, acne, pruritus allergic, rash maculo-papular, rash papular, rash pruritic, dermatitis.
Musculoskeletal and connective tissue disorders:
Uncommon: Arthralgia, muscle spasms, back pain, limb discomfort, neck pain.
Renal and urinary disorders:
Uncommon: Urine odour abnormal.
Reproductive system and breast disorders:
Uncommon: Vulvovaginal pruritus.
General disorders and administration site conditions:
Common: Fatigue, infusion site reactions (phlebitis).
Uncommon: Chills, infusion site pain, irritability, pyrexia, infusion related reaction, peripheral oedema.
Investigations:
Uncommon: Grip strength decreased, transaminases increased, white blood cell count decreased.

4.9. OVERDOSE:
In the event of overdose, Tedizolid Phosphate should be discontinued, and general supportive treatment given. Haemodialysis does not result in meaningful removal of tedizolid from systemic circulation. The highest single dose administered in clinical studies was 1,200mg. All adverse reactions at this dose level were mild or moderate in severity.

5. PHARMACOLOGICAL PROPERTIES
5.1. PHARMACODYNAMIC PROPERTIES:
Pharmacotherapeutic group: Antibacterials for systemic use, other antibacterials.
ATC code: J01XX11.
Mechanism of action: Tedizolid phosphate is an oxazolidinone phosphate prodrug. The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis. Tedizolid is primarily active against Gram-positive bacteria. Tedizolid is bacteriostatic against *enterococci*, *staphylococci*, and *streptococci* in vitro.
Resistance: The most commonly observed mutations in staphylococci and enterococci that result in oxazolidinone resistance are in one or more copies of the 23S rRNA genes (G2576U and T2500A). Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to tedizolid. A second resistance mechanism is encoded by a plasmid-borne and transposon associated chloramphenicol-florfenicol resistance *(cfr)* gene, conferring

resistance in staphylococci and enterococci to oxazolidinones, phenicols, lincosamides, pleuromutilins, streptogramin A and 16-membered macrolides. Due to a hydroxymethyl group in the C5 position, tedizolid retains activity against strains of Staphylococcus aureus that express the *cfr* gene in the absence of chromosomal mutations. The mechanism of action is different from that of non-oxazolidinone class antibacterial medicinal products; therefore, cross-resistance between tedizolid and other classes of antibacterial medicinal products is unlikely.

Antibacterial activity in combination with other antibacterial and antifungal agents: In vitro drug combination studies with tedizolid and amphotericin B, aztreonam, ceftazidime, ceftriaxone, ciprofloxacin, clindamycin, colistin, daptomycin, gentamicin, imipenem, ketoconazole, minocycline, piperacillin, rifampicin, terbinafine, trimethoprim/ sulfamethoxazole, and vancomycin indicate that neither synergy nor antagonism have been demonstrated.

Pharmacokinetic/pharmacodynamic relationship: The AUC/MIC ratio was the pharmacodynamic parameter shown to best correlate with efficacy in mouse thigh and lung *S. aureus* infection models. In a mouse thigh infection model of *S. aureus*, the antibacterial activity of tedizolid was reduced in the absence of granulocytes. The AUC/MIC ratio to achieve bacteriostasis in neutropenic mice was at least 16 times that in immunocompetent animals.

Clinical efficacy against specific pathogens: Efficacy has been demonstrated in clinical studies against the pathogens listed under each indication that were susceptible to tedizolid in vitro.

Acute bacterial skin and skin structure infections:

- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus*, *S. intermedius* and *S. constellatus*)

Antibacterial activity against other relevant pathogens: Clinical efficacy has not been established against the following pathogens although in vitro studies suggest that they would be susceptible to tedizolid in the absence of acquired mechanisms of resistance:

- *Staphylococcus lugdunensis*

5.2. PHARMACOKINETICS PROPERTIES:

Oral and intravenous tedizolid phosphate is a prodrug that is rapidly converted by phosphatases to tedizolid, the microbiologically active moiety.

Absorption: At steady state, tedizolid mean (SD) C_{max} values of 2.2 (0.6) and 3.0 (0.7) mcg/mL and AUC values of 25.6 (8.5) and 29.2 (6.2) mcg· h/mL were similar with oral and IV administration of tedizolid phosphate, respectively. The

absolute bioavailability of tedizolid is above 91%. Peak plasma tedizolid concentrations are achieved within approximately 3 hours after dosing after oral administration of tedizolid phosphate under fasted conditions. Peak concentrations (C_{max}) of tedizolid are reduced by approximately 26% and delayed by 6 hours when tedizolid phosphate is administered after a high-fat meal relative to fasted, while total exposure (AUC0-∞) is unchanged between fasted and fed conditions.

Distribution: The average binding of tedizolid to human plasma proteins is approximately 70-90%. The mean steady state volume of distribution of tedizolid in healthy adults (n=8) following a single intravenous dose of tedizolid phosphate 200mg ranged from 67 to 80 L.

Biotransformation: Tedizolid phosphate is converted by endogenous plasma and tissue phosphatases to the microbiologically active moiety, tedizolid. Other than tedizolid, which accounts for approximately 95% of the total radiocarbon AUC in plasma, there are no other significant circulating metabolites. When incubated with pooled human liver microsomes, tedizolid was stable suggesting that tedizolid is not a substrate for hepatic CYP450 enzymes. Multiple sulfotransferase (SULT) enzymes (SULT1A1, SULT1A2, and SULT2A1) are involved in the biotransformation of tedizolid, to form an inactive and non-circulating sulphate conjugate found in the excreta.

Elimination: Tedizolid is eliminated in excreta, primarily as a non-circulating sulphate conjugate. Following single oral administration of ^{14}C-labeled tedizolid phosphate under fasted conditions, the majority of elimination occurred via the liver with 81.5% of the radioactive dose recovered in faeces and 18% in urine, with most of the elimination (>85%) occurring within 96 hours. Less than 3% of tedizolid phosphate administered dose is excreted as active tedizolid. The elimination half-life of tedizolid is approximately 12 hours and the intravenous clearance is 6-7 L/h.

Linearity/non-linearity: Tedizolid demonstrated linear pharmacokinetics with regard to dose and time. The C_{max} and AUC of tedizolid increased approximately dose proportionally within the single oral dose range of 200mg to 1,200mg and across the intravenous dose range of 100mg to 400mg. Steady-state concentrations are achieved within 3 days and indicate modest active substance accumulation of approximately 30% following multiple once-daily oral or intravenous administration as predicted by a half-life of approximately 12 hours.

5.3. PRECLINICAL SAFETY DATA:

Long-term carcinogenicity studies have not been conducted with tedizolid phosphate. Repeated oral and intravenous dosing of tedizolid phosphate in rats in 1-month and 3-month toxicology studies produced dose- and time-dependent bone marrow hypocellularity (myeloid, erythroid, and megakaryocyte), with associated reduction in circulating RBCs, WBCs, and platelets. These effects

showed evidence of reversibility and occurred at plasma tedizolid exposure levels (AUC) ≥ 6-fold greater than the plasma exposure associated with the human therapeutic dose. In a 1-month immunotoxicology study in rats, repeated oral dosing of tedizolid phosphate was shown to significantly reduce splenic B cells and T cells and reduce plasma IgG titres. These effects occurred at plasma tedizolid exposure levels (AUC) ≥ 3-fold greater than the expected human plasma exposure associated with the therapeutic dose. A special neuropathology study was conducted in pigmented Long Evans rats administered tedizolid phosphate daily for up to 9 months. This study used sensitive morphologic evaluation of perfusion-fixed peripheral and central nervous system tissue. No evidence of neurotoxicity, including neurobehavioral changes or optic or peripheral neuropathy, was associated with tedizolid after 1, 3, 6 or 9 months of oral administration up to doses with plasma exposurelevels (AUC) up to 8-fold greater than the expected human plasma exposure at the oral therapeutic dose. Tedizolid phosphate was negative for genotoxicity in all in vitro assays (bacterial reverse mutation [Ames], Chinese hamster lung [CHL] cell chromosomal aberration) and in all in vivo tests (mouse bone marrow micronucleus, rat liver unscheduled DNA synthesis). Tedizolid, generated from tedizolid phosphate after metabolic activation (in vitro and in vivo), was also tested for genotoxicity. Tedizolid was positive in an in vitro CHL cell chromosomal aberration assay, but negative for genotoxicity in other in vitro assays (Ames, mouse lymphoma mutagenicity) and in vivo in a mouse bone marrow micronucleus assay. Tedizolid phosphate had no adverse effects on the fertility or reproductive performance of male rats, including spermatogenesis, at oral doses up to the maximum tested dose of 50mg/kg/day, or adult female rats at oral doses up to the maximum tested dose of 15mg/kg/day. These dose levels equate to exposure margins of ≥ 5.3-fold for males and ≥ 4.2-fold for females relative to tedizolid plasma AUC_{0-24} levels at the human oral therapeutic dose. Embryo-foetal development studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4-fold and 6-fold, respectively, those expected in humans. In embryo-foetal studies, tedizolid phosphate was shown to produce foetal developmental toxicities in mice and rats. Foetal developmental effects occurring in mice in the absence of maternal toxicity included reduced foetal weights and an increased incidence of costal cartilage fusion (an exacerbation of the normal genetic predisposition to sternal variations in the CD-1 strain of mice) at the high dose of 25mg/kg/day (4-fold the estimated human exposure level based on AUCs). In rats, decreased foetal weights and increased skeletal variations including reduced ossification of the sternabrae, vertebrae, and skull were observed at the high dose of 15mg/kg/day (6-fold the estimated human exposure based on AUCs) and were associated with maternal toxicity (reduced maternal body weights). The no observed adverse effect levels (NOAELs) for foetal toxicity in mice (5mg/kg/day) as well as maternal and foetal toxicity in rats (2.5mg/kg/day) were

associated with tedizolid plasma area under the curve (AUC) values approximately equivalent to the tedizolid AUC value associated with the oral human therapeutic dose. Tedizolid is excreted into the milk of lactating rats and the concentrations observed similar to those in maternal plasma.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS:

- Mannitol
- Sodium hydroxide
- Hydrochloric acid

6.2. INCOMPATIBILITIES:

This medicininal product must not be mixed with other medicinal products except Sterile Water for Injection and Sodium Chloride 0.9% Solution for Injection. Tedizolid Phosphate is incompatible with any solutions containing divalent cations (e.g., Ca2+, Mg2+), including Lactated Ringer's Injection and Hartmann's solution. Only limited data are available on the compatibility of Tedizolid Phosphate with other intravenous substances, therefore additives or other medicinal products should not be added to single use vials or infused simultaneously.

6.3. SHELF LIFE:

Unopened vial: See expiry on the pack.
Reconstituted solution: The reconstituted solution must be used immediately. If not, the reconstituted and diluted solution should be stored at room temperature or at 2-8°C and use within 24 hours.

6.4. SPECIAL PRECAUTIONS FOR STORAGE:

Do not store over 30°C, and protect from heat and moisture.
Improper storage may deteriorate the medicine.
The reconstituted solution must be used immediately. If not, the reconstituted and diluted solution should be stored at room temperature or at 2-8°C and use within 24 hours.
Keep out of reach of children.

6.5. NATURE AND CONTENTS OF CONTAINER:

Powder for Injection: Clear glass vial (USP Type-I) with chlorobutyl rubber stopper, sealed with flip off seal.
Water for Injection: Clear 4ml glass ampoule (USP Type-I).
Pack size is 1 vial & 1 ampoule.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL OF A USED PRODUCT:

Vials are intended for single use only. The reconstituted solution should be inspected visually for particulate matter prior to administration. Reconstituted

solution containing visible particles should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

6.7. DRUG PRODUCT SPECIFICATIONS:

Innovator's Specs.

7. REGISTRATION / MARKETING AUTHORISATION HOLDER

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, Off Hub River Road, S.I.T.E., Karachi-Pakistan
www.samipharma.com
Mfg Lic. No. 000072

8. REGISTRATION / MARKETING AUTHORISATION NUMBER(S)

126906

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

08th May, 2025

10. DATE OF REVISION OF THE TEXT

ٹیڈز® انجکشن
(ٹیڈیزولِڈ فاسفیٹ)

ہدایات:

خوراک ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
صرف ایک مرتبہ استعمال کے لئے ہے غیر استعمال شدہ دوا کو ضائع کر دیں۔
دوا کو ۳۰ ڈگری سینٹی گریڈ سے زیادہ درجہ حرارت پر نہ رکھیں،
گرمی اور نمی سے محفوظ رکھیں ورنہ دوا خراب ہو جائیگی۔
تیار شدہ انجکشن کو فوری استعمال کر لیں۔ اگر استعمال نہ ہو سکے تو تیار شدہ انجکشن کو کمرے کے درجہ حرارت یا
۲ سے ۸ ڈگری سینٹی گریڈ پر رکھیں اور ۲۴ گھنٹے کے اندر استعمال کر لیں۔