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

TEDIREX 200

1. **Generic Name**

   Tedizolid Phosphate Tablets 200 mg

2. **Qualitative and quantitative Composition:**

   TEDIREX 200

   Each film coated tablet contains:

   Tedizolid Phosphate……200 mg

   Excipients……. q.s.

   Colours: Ferric Oxide USP-NF Yellow and Titanium Dioxide I.P.

   The excipients used are Mannitol, Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Crospovidone, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Polyethylene Glycol, Talc and Ferric Oxide Yellow.

3. **Dosage form and strength**

   Dosage form: Tablet

   Strength: 200 mg

4. **Clinical particulars**

4.1. Therapeutic indication

Tedizolid is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and adolescents 12 years of age and older.

4.2. Posology and method of administration

Posology

Tedizolid phosphate film-coated tablets 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 200 mg once daily for 6 days.

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.

Special Patient Populations

Elderly Patients

No dosage adjustment is required. The clinical experience in patients ≥75 years is limited.

Paediatric Patients

The safety and efficacy of tedizolid phosphate in children below 12 years of age have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology for children below 12 years of age can be made.

Impaired Renal Function

No dosage adjustment is required.

Impaired Hepatic Function

No dosage adjustment is required.

Method of administration

Patients should be informed that Tedizolid tablets may be taken with or without food and without any dietary restrictions.

4.3. Contraindications

Hypersensitivity to Tedizolid or any of its components.

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 revaluated. 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 another member of the oxazolidinone class together with serotonergic agents have been reported.

There is no Phase 3 clinical experience in patients with co-administration of tedizolid phosphate with serotonergic agents such as selective serotonin re-uptake inhibitors [SSRI], serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, MAO inhibitors, triptans, and other medicines with potential adrenergic or serotonergic activity.

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.

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.

4.5. Drugs interactions

Pharmacokinetic interactions

In a clinical study comparing the single dose (10 mg) pharmacokinetics of rosuvastatin (Breast Cancer Resistant Protein [BCRP] substrate) alone or in combination with tedizolid phosphate (once-daily 200 mg oral dose), rosuvastatin AUC and Cmax increased by approximately 70% and 55%, respectively, when coadministered with tedizolid phosphate. Therefore, orally administered tedizolid phosphate can result in inhibition of BCRP at the intestinal level. If possible, an interruption of the coadministered 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.

In a clinical study comparing the single dose (2 mg) pharmacokinetics of midazolam (CYP3A4 substrate) alone or in combination with tedizolid phosphate (once-daily 200 mg oral dose for 10 days), midazolam AUC and Cmax when co-administered with tedizolid phosphate were 81% and 83% of midazolam AUC and Cmax when administered alone, respectively. This effect is not clinically meaningful, and no dose adjustment for co-administered CYP3A4 substrates is necessary during tedizolid phosphate treatment.

Pharmacodynamic interactions

Monoamine oxidase inhibition Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) in vitro; however, no interaction is anticipated when comparing the IC50 for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies to determine effects of 200 mg 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.

4.6. Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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.

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.

4.7. Effects on ability to drive and use machines

Tedizolid 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

Summary of the safety profile

Adults

Adverse reactions were evaluated for 1425 adult patients treated with tedizolid phosphate in two Phase 2 and four Phase 3 clinical trials (three Phase 3 trials for 6 days of therapy and one Phase 3 trial for 7-21 days of therapy). The median age of adult patients treated with tedizolid phosphate in the Phase 2 and Phase 3 trials was 44 years, ranging between 17 and 94 years old. The majority of adult patients treated with tedizolid phosphate were male (66%) and White (67%).

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation in Adults

Serious adverse reactions occurred in 37/1425 (2.6%) of adult patients treated with tedizolid phosphate and in 25/1000 (2.5%) of adult patients treated with the comparator. Tedizolid phosphate was discontinued due to an adverse reaction in 14/1425 (1%) of adult patients and the comparator was discontinued due to an adverse reaction in 13/1000 (1.3%) of adult patients.

Most Common Adverse Reactions in Adults

The most common adverse reactions in adult patients treated with tedizolid phosphate were nausea (7.1%), headache (4.5%), diarrhea (3.6%), vomiting (2.7%), and dizziness (1.6%). The median time of onset of adverse reactions was 5 days for both tedizolid phosphate and linezolid with 12% occurring on the second day of treatment in both treatment groups.

The following selected adverse reactions were reported in tedizolid phosphate -treated adult patients at a rate of less than 2% in these clinical trials:

Blood and Lymphatic System Disorders: Anemia

Cardiovascular: Palpitations, tachycardia

Eye Disorders: Asthenopia, vision blurred, visual impairment, vitreous floaters.

Immune System Disorders: Drug hypersensitivity

Infections and Infestations: Clostridioides difficile colitis, oral candidiasis, vulvovaginal mycotic infection

Investigations: Hepatic transaminases increased (ALT increased, AST increased), gamma-glutamyl transferase (GGT) increased, white blood cell count decreased

Nervous System Disorders: Hypoesthesia, paresthesia, VIIth nerve paralysis

Psychiatric Disorders: Insomnia

Skin and Subcutaneous Tissue Disorders: Pruritus, urticaria, dermatitis

Vascular Disorders: Flushing, hypertension

Postmarketing Experience

The following adverse reactions have been identified during post approval use of tedizolid phosphate. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Blood and Lymphatic System Disorders: Thrombocytopenia

Reporting of 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. Report suspected adverse reactions via any point of contact available at www.torrentpharma.com.

4.9. Overdose

In the event of overdose, Tedizolid should be discontinued, and general supportive treatment given. Haemodialysis does not result in meaningful removal of tedizolid from systemic circulation.

5. Pharmacological properties

5.1. Mechanism of Action

Tedizolid is an antibacterial drug. The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis. Tedizolid inhibits bacterial protein synthesis through a mechanism of action different from that of other non-oxazolidinone class antibacterial drugs; therefore, cross-resistance between tedizolid and other classes of antibacterial drugs is unlikely. The results of in vitro time-kill studies show that tedizolid is bacteriostatic against enterococci, staphylococci, and streptococci.

5.2. Pharmacodynamic properties

The AUC/minimum inhibitory concentration (MIC) was shown to best correlate with tedizolid activity in animal infection models. In the mouse thigh infection model of S. aureus, antistaphylococcal killing activity was impacted by the presence of granulocytes. In granulocytopenic mice (neutrophil count <100 cells/mL), bacterial stasis was achieved at a human-equivalent dose of approximately 2000 mg/day, whereas, in non-granulocytopenic animals, stasis was achieved at a human-equivalent dose of approximately 100 mg/day. The safety and efficacy of tedizolid for the treatment of neutropenic patients (neutrophil counts <1000 cells/mm3) have not been evaluated.

Cardiac Electrophysiology

In a randomized, positive-and placebo-controlled crossover thorough QTc study, 48 enrolled subjects were administered a single oral dose of at a therapeutic dose of 200 mg, Tedizolid at a supratherapeutic dose of 1200 mg, placebo, and a positive control; no significant effects of tedizolid on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected. Therefore, tedizolid does not affect cardiac repolarization.

In the event of overdose, Tedizolid 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 1,200 mg. All adverse reactions at this dose level were mild or moderate in severity.

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 16membered 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.

5.3. Pharmacokinetic properties

Tedizolid phosphate is a prodrug that is converted by phosphatases to tedizolid, the microbiologically active moiety, following oral and intravenous administration. Only the pharmacokinetic profile of tedizolid is discussed further due to negligible systemic exposure of tedizolid phosphate following oral and intravenous administration. Following multiple once daily oral or intravenous administration, steady-state concentrations are achieved within approximately three days with tedizolid accumulation of approximately 30% (tedizolid half-life of approximately 12 hours). Pharmacokinetic (PK) parameters of tedizolid following oral and intravenous administration of 200 mg once daily tedizolid phosphate are shown in the Table.

Table: Mean (Standard Deviation) Tedizolid Pharmacokinetic Parameters Following Single and Multiple Oral and Intravenous Administration of 200 mg Once-Daily Tedizolid Phosphate

Pharmacokinetic Parameters of Tedizolid*	Oral		Intravenous	
	Single dose	Steady state	Single dose	Steady state
C_{max} (mcg/mL)	2.0 (0.7)	2.2 (0.6)	2.3 (0.6)	3.0 (0.7)
T_{max} (hr)†	2.5 (1.0 - 8.0)	3.5 (1.0 - 6.0)	1.1 (0.9 - 1.5)	1.2 (0.9 - 1.5)
AUC (mcg·hr/mL) ‡	23.8 (6.8)	25.6 (8.4)	26.6 (5.2)	29.2 (6.2)
CL or CL/F (L/hr)	6.9 (1.7)	8.4 (2.1)	6.4 (1.2)	5.9 (1.4)

C_{max}, maximum concentration; T_{max}, time to reach C_{max}; AUC, area under the concentration-time curve; CL, systemic clearance; CL/F, apparent oral clearance.
† Median (range) ‡
AUC is $AUC_{0-\infty}$ (AUC from time 0 to infinity) for single-dose administration and AUC_{0-24} (AUC from time 0 to 24 hours) for multiple-dose administration.

Absorption

Peak plasma tedizolid concentrations are achieved within approximately 3 hours following oral administration under fasting conditions or at the end of the 1-hour intravenous infusion of tedizolid phosphate. The absolute bioavailability is approximately 91% and no dosage adjustment is necessary between intravenous and oral administration.

Tedizolid phosphate (oral) may be administered with or without food as total systemic exposure ($AUC_{0-\infty}$) is unchanged between fasted and fed (high-fat, high-calorie) conditions.

Distribution

Protein binding of tedizolid to human plasma proteins is approximately 70 to 90%. The mean steady state volume of distribution of tedizolid in healthy adults following a single intravenous dose of tedizolid phosphate 200 mg ranged from 67 to 80 L (approximately twice total body water). Tedizolid penetrates into the interstitial space fluid of adipose and skeletal muscle tissue with exposure similar to free drug exposure in plasma.

Metabolism

Other than tedizolid, which accounts for approximately 95% of the total radiocarbon AUC in plasma, there are no other significant circulating metabolites in humans. There was no degradation of tedizolid in human liver microsomes indicating tedizolid is unlikely to be a substrate for hepatic CYP450 enzymes.

Excretion

Following single oral administration of ^{14}C-labeled tedizolid phosphate under fasted conditions, the majority of elimination occurred via the liver, with 82% of the radioactive dose recovered in feces and 18% in urine, primarily as a non-circulating and microbiologically inactive sulfate conjugate. Most of the elimination of tedizolid (>85%) occurs within 96 hours. Less than 3% of the tedizolid phosphate-administered dose is excreted in feces and urine as unchanged tedizolid.

Special Populations

Impaired Renal Function

Following administration of a single 200 mg IV dose of tedizolid phosphate to 8 subjects with severe renal impairment defined as eGFR <30 mL/min, the C_{max} was basically unchanged and $AUC_{0-\infty}$ was changed by less than 10% compared to 8 matched healthy subject controls. Haemodialysis does not result in meaningful removal of tedizolid from systemic circulation, as assessed in subjects with end-stage renal disease (eGFR <15 mL/min). The eGFR was calculated using the MDRD4 equation.

Impaired Hepatic Function

Following administration of a single 200 mg oral dose of tedizolid phosphate, the pharmacokinetics of tedizolid are not altered in patients with moderate (n=8) or severe (n=8) hepatic impairment (Child-Pugh Class B and C).

Elderly population

Following administration of a single 200 mg oral dose of tedizolid phosphate, the pharmacokinetics of tedizolid are not altered in patients with moderate (n=8) or severe (n=8) hepatic impairment (Child-Pugh Class B and C).

Paediatric population

The pharmacokinetics of tedizolid were evaluated in adolescents (12 to 17 years; n=20) following administration of a single oral or IV dose of tedizolid phosphate 200 mg and in adolescents (12 to <18 years; n=91) receiving tedizolid phosphate 200 mg IV or oral every 24 hours for 6 days. The estimated mean C_{max} and AUC_{0-24h} at steady state for tedizolid in adolescents were 3.37 µg/mL and 30.8 µg·h/mL which were similar to adults.

Gender

The impact of gender on the pharmacokinetics of tedizolid phosphate was evaluated in healthy males and females in clinical studies and in a population pharmacokinetics analysis. The pharmacokinetics of tedizolid were similar in males and females.

Drug Interaction Studies

Drug metabolizing enzymes

In vitro studies in human liver microsomes indicate that tedizolid phosphate and tedizolid do not significantly inhibit metabolism mediated by any of the following CYP isoenzymes (CYP1A2, CYP2C19, CYP2A6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4). Tedizolid did not alter activity of selected CYP isoenzymes, but induction of CYP3A4 mRNA was observed

in vitro in hepatocytes. A clinical study comparing the single dose (2 mg) pharmacokinetics of midazolam (CYP3A4 substrate) alone or in combination with tedizolid phosphate (once-daily 200 mg oral dose for 10 days), demonstrated no clinically meaningful difference in midazolam Cmax or AUC. No dose adjustment is necessary for co-administered CYP3A4 substrates during treatment with Tedizolid.

Membrane transporters

The potential for tedizolid or tedizolid phosphate to inhibit transport of probe substrates of important drug uptake (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2) and efflux transporters (P-gp and BCRP) was tested in vitro. No clinically relevant interactions are expected to occur with these transporters, with the administration of the parenteral formulation.

In a clinical study comparing the single dose (10 mg) pharmacokinetics of rosuvastatin (BCRP substrate) alone or in combination with the oral administration of tedizolid phosphate 200 mg, rosuvastatin AUC and Cmax increased by approximately 70% and 55%, respectively, when coadministered with Tedizolid. Therefore, orally administered Tedizolid can result in inhibition of BCRP at the intestinal level.

Monoamine oxidase inhibition

Tedizolid is a reversible inhibitor of MAO in vitro; however, no interaction is anticipated when comparing the IC_{50} and the anticipated plasma exposures in man. No evidence of MAO-A inhibition was observed in Phase 1 studies specifically designed to investigate the potential for this interaction.

Adrenergic agents

Two placebo-controlled crossover studies were conducted to assess the potential of 200 mg oral tedizolid phosphate at steady state to enhance pressor responses to pseudoephedrine and tyramine in healthy individuals. No meaningful changes in blood pressure or heart rate were seen with pseudoephedrine. The median tyramine dose required to cause an increase in systolic blood pressure of ≥30 mmHg from pre-dose baseline was 325 mg with tedizolid phosphate compared to 425 mg with placebo. Administration of Tedizolid with tyramine-rich foods (i.e., containing tyramine levels of approximately 100 mg) would not be expected to elicit a pressor response.

Serotonergic agents

Serotonergic effects at doses of tedizolid phosphate up to 30-fold above the human equivalent dose did not differ from vehicle control in a mouse model that predicts brain serotonergic activity. There are limited data in patients on the interaction between serotonergic agents and tedizolid phosphate. In Phase 3 studies, subjects taking serotonergic agents including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, and serotonin 5-hydroxytryptamine (5-HT1) receptor agonists (triptans), meperidine, or buspirone were excluded.

6. Nonclinical properties

6.1. Animal Toxicology or Pharmacology

Carcinogenesis

Long-term carcinogenicity studies have not been conducted with tedizolid phosphate.

Immunogenicity

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.

Neurotoxicity

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 exposure levels (AUC) up to 8-fold greater than the expected human plasma exposure at the oral therapeutic dose.

Mutagenicity

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.

Impairment of Fertility

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 50 mg/kg/day, or adult female rats at oral doses up to the maximum tested dose of 15 mg/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 $AUC_{0\text{-}24}$ levels at the human oral therapeutic dose.

Embryo-fetal 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-fetal studies, tedizolid phosphate was shown to produce fetal developmental toxicities in mice and rats. Fetal developmental effects occurring in mice in the absence of maternal toxicity included reduced fetal 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 25 mg/kg/day (4-fold the estimated human exposure level based on AUCs). In rats, decreased fetal weights and increased skeletal variations including reduced ossification of the sternabrae, vertebrae, and skull were observed at the high dose of 15 mg/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 fetal toxicity in mice (5 mg/kg/day) as well as maternal and fetal toxicity in rats (2.5 mg/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.

Animal Toxicology and/or Pharmacology

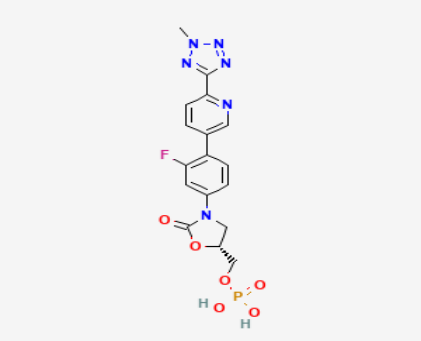
Repeated-oral and intravenous dosing of tedizolid phosphate in rats in 1-month and 3-month toxicology studies produced dose-and time-dependent bone marrow hypocellularity (myeloid,

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 titers. These effects occurred at plasma tedizolid exposure levels (AUC) ≥3-fold greater than the expected human plasma exposure associated with the therapeutic dose.

7. Description

Tedizolid Phosphate:

Myo-inositol is [(5R)-3-[3-fluoro-4-[6-(2-methyltetrazol-5-yl)-3-pyridinyl] phenyl]-2-oxo-1,3-oxazolidin-5-yl] methyl dihydrogen phosphate. The empirical formula is $C_{17}H_{16}FN_6O_6P$ and the molecular weight is 450.3 g/mol. The chemical structural formula is:



TEDIREX 200

Tedizolid Phosphate Tablets is yellow coloured, oval shaped, film coated tablets plain on both sides. The excipients used are Mannitol, Microcrystalline Cellulose, Polyvinyl Pyrrolidone, Crospovidone, Magnesium Stearate, Polyvinyl Alcohol, Titanium Dioxide, Polyethylene Glycol, Talc and Ferric Oxide Yellow.

8. Pharmaceutical particulars

8.1. Incompatibilities

Not applicable

8.2. Shelf-life

Do not use later than date of expiry.

8.3. Packaging information

TEDIREX 200 is available in the pack of 6 Tablets.

8.4. Storage and handing instructions

Store in a dry, well-ventilated place at a temperature not exceeding 30°C.
Keep out of reach of Children.

9. Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant

- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10. Details of manufacturer

Hetero Labs Limited (Unit-II)
Village: Kalyanpur,
Chakkan Road,
Tehsil: Baddi, Distt.: Solan,
Himachal Pradesh – 173 205

11. Details of permission or licence number with date

Mfg. Licence No: MNB/09/780 issued on. 03.10.2025

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/TEDIREX 200mg/JAN-2026/01/PI