PRODUCT MONOGRAPH

PrSIVEXTRO™

tedizolid phosphate tablets
200 mg

tedizolid phosphate for injection
200 mg/vial

Antibacterial Agent

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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION....3
SUMMARY PRODUCT INFORMATION....3
INDICATIONS AND CLINICAL USE....3
CONTRAINDICATIONS....4
WARNINGS AND PRECAUTIONS....4
ADVERSE REACTIONS....6
DRUG INTERACTIONS....10
DOSAGE AND ADMINISTRATION....11
OVERDOSAGE....14
ACTION AND CLINICAL PHARMACOLOGY....14
STORAGE AND STABILITY....17
SPECIAL HANDLING INSTRUCTIONS....18
DOSAGE FORMS, COMPOSITION AND PACKAGING....18

PART II: SCIENTIFIC INFORMATION....19
PHARMACEUTICAL INFORMATION....19
CLINICAL TRIALS....20
DETAILED PHARMACOLOGY....24
MICROBIOLOGY....26
TOXICOLOGY....28
REFERENCES....30

PART III: CONSUMER INFORMATION....31

PrSIVEXTRO™

Tedizolid Phosphate

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet, 200 mg	None *For a complete listing see Dosage Forms, Composition and Packaging section.*
Intravenous injection	Lyophilized powder, 200 mg/vial	None *For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

SIVEXTRO™ (tedizolid phosphate) tablets and SIVEXTRO™ for injection are indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible strains of the following gram-positive microorganisms in adults 18 years of age and older:

Staphylococcus aureus (including methicillin-resistant [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus* Group (including *Streptococcus anginosus*, *Streptococcus intermedius,* and *Streptococcus constellatus*).

SIVEXTRO is not active against gram-negative bacteria commonly associated with ABSSSI; therefore, combination therapy may be clinically indicated if the infection is polymicrobial and includes a suspected or documented gram-negative pathogen.

SIVEXTRO has been studied in the treatment of cellulitis/erysipelas, major cutaneous abscesses, or wound infections only. Other types of complicated skin infections (including diabetic foot ulcer, necrotizing fasciitis, or decubitus ulcer) have not been studied.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of SIVEXTRO and other antibacterial drugs, SIVEXTRO should be used only to treat ABSSSI that are proven or strongly suspected to be caused by gram-positive susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. SIVEXTRO may be initiated as empiric therapy in the absence

of such data. Local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

Geriatrics (≥65 years of age):
No dose adjustment is required in patients 65 years and older. No overall differences in safety, efficacy, or pharmacokinetics were observed between these subjects and younger adult subjects.

Pediatrics (<18 years of age):
Safety and efficacy of SIVEXTRO in children less than 18 years of age have not been established.

CONTRAINDICATIONS

Patients who are hypersensitive to tedizolid phosphate or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph.

WARNINGS AND PRECAUTIONS

General
The safety and efficacy of SIVEXTRO at doses higher than the recommended dose (200 mg once daily) and treatment durations longer than 6 days have not been established.

Prescribing SIVEXTRO in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

SIVEXTRO is not active against gram-negative bacteria and is not indicated for the treatment of infections caused by gram-negative bacteria. Adjunct specific gram-negative therapy should be initiated immediately if a concomitant gram-negative pathogen is documented or suspected.

Effects on Ability to Drive and use Machines
There have been no formal studies to evaluate changes in cognitive ability or the ability to drive or operate machinery while receiving SIVEXTRO. SIVEXTRO may cause dizziness, fatigue or, uncommonly, somnolence which could influence the ability to drive or use machines.

Lactic Acidosis
Tedizolid inhibits mitochondrial protein synthesis. Lactic acidosis has been reported with the use of another member of the oxazolidinone antibacterial class. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or low bicarbonate levels while receiving SIVEXTRO should receive immediate medical attention (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Neutropenia
The safety and efficacy of SIVEXTRO in patients with neutropenia (neutrophil counts <1000 cells/mm^3) have not been evaluated. In an animal model of infection, the antibacterial activity of SIVEXTRO was reduced in the absence of granulocytes. Alternative therapies should be considered when treating patients with neutropenia and acute bacterial skin and skin structure infections (see **DETAILED PHARMACOLOGY, Animal Pharmacology**).

Monoamine Oxidase Inhibition
Tedizolid is a reversible, non-selective inhibitor of monoamine oxidase (MAO) *in vitro*. Therefore, tedizolid has the potential for interaction with adrenergic and serotonergic agents. However, nonclinical and Phase 1 clinical studies of tedizolid did not demonstrate evidence of MAO inhibition *in vivo*. 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 SIVEXTRO with serotonergic agents such as selective serotonin re-uptake inhibitors [SSRI], serotonin norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants, MAO inhibitors, triptans, and other medications with potential adrenergic or serotonergic activity (see **DRUG INTERACTIONS**).

Carcinogenesis and Mutagenesis
Long-term carcinogenicity studies have not been conducted with tedizolid phosphate due to the short duration of proposed therapeutic use.

Gastrointestinal
***Clostridium difficile*-Associated Diarrhea**
Clostridium difficile-associated diarrhea (CDAD) has been reported for nearly all systemic antibacterial agents including SIVEXTRO. CDAD may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit 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 severe diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, antibacterials not directed against *C. difficile* should be discontinued, if possible. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated (see **ADVERSE REACTIONS**).

Peripheral and Optic Neuropathy
Peripheral and optic neuropathy has been reported in patients treated with a member of the oxazolidinone class for longer than 28 days. In Phase 3 trials, reported adverse reactions for

peripheral neuropathy and optic nerve disorders were similar between both treatment arms. No data are available for patients exposed to SIVEXTRO for longer than 6 days (see **ADVERSE REACTIONS**).

Special Populations

Pregnant Women: No clinical studies have been conducted with SIVEXTRO in pregnant women. Studies in mice, rats, and rabbits have demonstrated developmental effects. SIVEXTRO should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and fetus (see **TOXICOLOGY, Reproduction and Development Toxicology**).

Nursing Women: Tedizolid is excreted in the breast milk of rats. It is not known whether tedizolid is excreted in human milk. Nursing woman should be advised to discontinue breast feeding while receiving SIVEXTRO treatment.

Women of Childbearing Potential: Women of childbearing potential must use reliable contraception while taking SIVEXTRO. It is currently unknown whether SIVEXTRO may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives must use an additional method of contraception (see **DRUG INTERACTIONS**).

Geriatrics (≥65 years of age): Of the 662 patients treated with SIVEXTRO in Phase 3 clinical trials, 72 (11%) were ≥65 years and 24 (4%) were ≥75 years. Safety data of SIVEXTRO is available in limited number of patients with greater than 75 years. Adverse reactions were slightly higher in elderly patients ≥75 (years) than <75 years (see **ACTION AND CLINICAL PHARMACOLOGY**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Safety data are available from a number of controlled and uncontrolled studies in which 1050 patients with acute bacterial skin and skin structure infections (ABSSSI) and 438 healthy subjects were exposed to SIVEXTRO.

The most common adverse drug reactions (ADRs) occurring in patients receiving SIVEXTRO in two Phase 3 controlled clinical trials were nausea, headache, diarrhea, and vomiting. Treatment discontinuations due to ADRs occurred in 3/662 (0.5%) of patients receiving SIVEXTRO and 6/662 (0.9%) receiving linezolid, with the most common reactions leading to discontinuations for both treatments being gastrointestinal disorders including vomiting and diarrhea. In the controlled studies, there were no serious adverse events that were considered by the Investigator to be related to SIVEXTRO.

In Phase 1 and Phase 2 studies, including doses other than the 200 mg therapeutic dose, the most common ADRs in subjects receiving SIVEXTRO were headache, diarrhea, and nausea. Treatment discontinuations due to ADRs occurred in 13/438 (3.0%) of subjects receiving SIVEXTRO and there were no serious adverse events that were considered by the Investigator to

be related to SIVEXTRO. Increased adverse reactions were reported in a Phase 2 dose-ranging study in patients receiving 400 mg once daily oral tedizolid phosphate di-sodium.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

SIVEXTRO was evaluated in adults aged 18 years or more in two Phase 3 comparator-controlled, double-blind, non-inferiority clinical trials, in which a total of 662 patients were treated with SIVEXTRO (200 mg administered once daily) for 6 days and 662 patients were treated with linezolid (600 mg administered every 12 hours) for 10 days. Among all treated patients in the controlled studies, the overall incidence of adverse drug reactions (defined as treatment emergent adverse events considered by the investigator as probably, possibly, or definitely related to the study drug) was 22.4% (148 patients) in the SIVEXTRO group and 27.9% (185 patients) in the active comparator group. The safety profile was similar when comparing patients receiving intravenous SIVEXTRO alone to patients who received oral administration alone, except for a higher reported rate of gastrointestinal disorders associated with oral administration. Table 1 lists adverse drug reactions occurring at a rate of ≥1% in the pooled Phase 3 ABSSSI clinical trials.

Table 1 Adverse Drug Reactions with ≥1% Incidence in the SIVEXTRO group in the Pooled Phase 3 Controlled ABSSSI Studies

System Organ Class Preferred Term	SIVEXTRO (N=662) n (%)	Active Comparator (N=662) n (%)
Number (%) of Patients with at least one ADR	101 (15.3)	134 (20.2)
Gastrointestinal Disorders	84 (12.7)	122 (18.4)
Nausea	46 (6.9)	65 (9.8)
Diarrhea	21 (3.2)	31 (4.7)
Vomiting	15 (2.3)	32 (4.8)
Nervous System Disorders	36 (5.4)	41 (6.2)
Headache	23 (3.5)	22 (3.3)
Dizziness	8 (1.2)	12 (1.8)
Skin And Subcutaneous Tissue Disorders	29 (4.4)	22 (3.3)
Pruritus Generalized	11 (1.7)	7 (1.1)
General Disorders And Administration Site Conditions	15 (2.3)	17 (2.6)
Fatigue	7 (1.1)	8 (1.2)

Note**:** A patient with an event coding to the same System Organ Class (SOC) or Preferred Term (PT) on more than 1 occasion is only counted 1 time for that SOC and PT.

Less Common Clinical Trial Adverse Drug Reactions (<1%)

Adverse drug reactions occurring at a rate of <1%, in patients treated with SIVEXTRO in Phase 3 clinical trials are listed below by body system.

Blood and Lymphatic Disorders: anemia, lymphadenopathy.

Cardiovascular: bradycardia, tachycardia, increased blood pressure (palpitations).

Eye Disorders: asthenopia, vision blurred, visual impairment, vitreous floaters, visual acuity reduced.

Gastrointestinal Disorders: abdominal discomfort, *Clostridium difficile* colitis, constipation, abdominal pain, dry mouth, dyspepsia, retching, haematochezia, gastrooesophageal reflux disease, flatulence, abdominal pain upper.

General Disorders and Administration Site Conditions: chills, infusion site pain, infusion site phlebitis, pyrexia, oedema peripheral, infusion related reaction, irritability.

Immune System Disorders: drug hypersensitivity.

Infections and Infestations: oral candidiasis, fungal infection, vulvovaginal mycotic infection, vulvovaginal candidiasis, dermatophytosis, respiratory tract infection.

Investigations: grip strength decreased, transaminases increased, white blood cell count decreased.

Metabolism and Nutrition Disorders: dehydration, diabetes mellitus inadequate control, hyperkalaemia.

Musculoskeletal and Connective Tissue Disorders: arthralgia, limb discomfort, neck pain, back pain, muscle spasms.

Nervous System Disorders: hypoaesthesia, VIIth nerve paresthesia, somnolence, dysgeusia, paraesthesia, tremor.

Psychiatric Disorders: insomnia, nightmare, anxiety, sleep disorder.

Renal and Urinary Disorders: urine odour abnormal.

Reproductive System and Breast Disorders: vulvovaginal pruritus.

Respiratory, Thoracic and Mediastinal Disorders: cough, nasal dryness, pulmonary congestion.

Skin and Subcutaneous Tissue Disorders: hyperhidrosis, pruritus, rash, urticaria, alopecia, rash generalized, rash papular, rash maculo-papular, pruritus allergic, acne, rash erythematous.

Vascular Disorders: hypertension, flushing, hot flush.

Abnormal Hematologic and Clinical Chemistry Findings

Hematology laboratory abnormalities that were determined to be potentially clinically significant in the pooled Phase 3 ABSSSI clinical trials are provided in Table 2.

Table 2 Potentially Clinically Significant Lowest Laboratory Values in the Pooled Phase 3 ABSSSI Clinical Trials

Laboratory Assay	Potentially Clinically Significant Values*†	
	SIVEXTRO (N=618)‡	Active Comparator (N=617)
Hemoglobin (<10.1 g/dL [M]) (<9 g/dL [F])	3.1%	3.7%
Platelet count (<112 × 10^3/mm^3)	2.3%	4.9%
Absolute neutrophil count (<0.8 × 10^3/mm^3)	0.5%	0.6%

M = male; F = female

* <75% (<50% for absolute neutrophil count) of lower limit of normal (LLN) for values normal at baseline

† Represents lowest abnormal post-baseline value through the last dose of active drug

‡ Number of patients with non-missing laboratory values

Myelosuppression

Phase 1 studies conducted in healthy adults exposed to SIVEXTRO for 21 days demonstrated a possible dose and duration effect on hematologic parameters beyond 6 days of treatment. In the Phase 3 trials, clinically significant changes in neutrophil and hemoglobin were generally similar for both treatment arms, but fewer patients had substantially abnormal platelet values in the SIVEXTRO arm than in the active comparator (linezolid) arm (see Table 2; **TOXICOLOGY, General Toxicology, Immunotoxicity**).

Post-Market Adverse Drug Reactions

Post-market adverse reactions to health products are considered to be suspicious, as a definite causal association often cannot be determined. Spontaneous reports of adverse reactions cannot be used to estimate the incidence of adverse reactions because adverse reactions remain underreported and patient exposure is unknown.

Nervous System Disorders: severe vomiting.

DRUG INTERACTIONS

Overview

No clinical metabolic drug-drug interaction or membrane transporter studies were conducted with SIVEXTRO. Based on *in vitro* results, there is a risk for enzyme induction by tedizolid phosphate. This may result in reduced efficacy of co-administered medicinal products that are narrow substrates of CYP3A4 (such as oral midazolam, cyclosporine, fentanyl, quinidine, sirolimus, and tacrolimus), CYP2B6 (efavirenz), CYP2C9 (warfarin), and P-gp (digoxin). The enzyme induction by tedizolid phosphate may also reduce the efficacy of oral hormonal contraceptives (e.g., birth control pills, skin patches, implants, and certain intrauterine devices [IUDs]).

Tedizolid is an inhibitor of monoamine oxidase (MAO) *in vitro*.

Drug-Drug Interactions

Drug Metabolizing Enzymes

In vitro, tedizolid or tedizolid phosphate did not demonstrate any clinically relevant CYP inhibition of selected risk for cytochrome P450 isoenzymes (CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4).

Based on *in vitro* results, there is a risk for CYP3A4 enzyme induction by tedizolid phosphate. Therefore, a potential risk to cause reduced efficacy of co-administered medicinal products that are narrow substrates of CYP3A4 (such as oral midazolam, triazolam, alfentanil, cyclosporine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), CYP2B6 (efavirenz), CYP2C9 (warfarin), and P-gp (digoxin) cannot be excluded.

Membrane Transporters

Potential for tedizolid or SIVEXTRO to inhibit transport substrates of important drug uptake (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2) and efflux transporters (P-gp and BCRP was tested *in vitro*. There is a potential for tedizolid phosphate to inhibit organic anion transporter (OATP1B1) based on *in vitro* data. Tedizolid inhibited OATP1B1 by ~30% at 30 μM. The *in vivo* relevance is unknown. The OATP1B1 inhibition could result in increased exposure of medicinal products such as statins (atorvastatin, fluvastatin, pitavastatin, and lovastatin), repaglinide, bosentan, valsartan, olmesartan, and glyburide.

There is a potential for interaction between oral tedizolid phosphate and orally administered substrates of BCRP. The BCRP inhibition could result in increased exposure of medicinal products such as imatinib, lapatinib, methotrexate, pitavastatin, rosuvastatin, sulfasalazine, and topotecan. If possible, an intermission of the co-administered medicinal product should be considered during the six days of treatment with tedizolid phosphate.

Monoamine Oxidase Inhibition

Tedizolid is a reversible inhibitor of MAO *in vitro*. SIVEXTRO interaction with MAO inhibitors could not be evaluated in patients with ABSSSI because patients on medicinal products which inhibit monoamine oxidases A or B (e.g., phenylzine, isocarboxazid) or

tyramine-rich foods were excluded from the trials. Placebo-controlled crossover studies with 200 mg oral SIVEXTRO at steady state did not demonstrate enhanced pressor responses to pseudoephedrine and tyramine in healthy individuals. No meaningful changes in blood pressure or heart rate were seen with pseudoephedrine (see **DETAILED PHARMACOLOGY, Safety Pharmacology**).

Serotonergic Agents
There are limited data in patients on the interaction between serotonergic agents and SIVEXTRO. 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. SIVEXTRO at doses of up to 30-fold above human equivalent did not differ from vehicle control in a mouse model that predicts serotonergic activity (see **DETAILED PHARMACOLOGY, Secondary Pharmacodynamics**).

Drug-Food Interactions
Interactions with food have not been established with the tablet formulation proposed for market. SIVEXTRO may be given without regard to timing of meals. In a study conducted with the developmental formulation of the drug, the total exposure ($AUC_{0-\infty}$) remained unchanged between fasted or fed (high-fat, high-calorie meal) conditions with the absorption (C_{max}) decreased by about 26% in fed subjects.

In a placebo-controlled study with concomitant administration of 200 mg oral SIVEXTRO with dietary tyramine, the median tyramine dose required to cause an increase in systolic blood pressure of ≥30 mmHg from pre-dose baseline was 325 mg with SIVEXTRO compared to 425 mg with placebo. Administration of SIVEXTRO with tyramine-rich foods (i.e., containing tyramine levels of approximately 100 mg) would not be expected to elicit a pressor response.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- 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 cellulitis/erysipelas, major cutaneous abscesses, and wound infections only. Other types of skin infections have not been studied.

- There is no experience with SIVEXTRO in the treatment of ABSSSI with severe sepsis or septic shock.
- SIVEXTRO is not active against gram-negative bacteria commonly associated with ABSSSI therefore combination therapy may be clinically indicated if the infection is polymicrobial and includes a suspected or documented gram-negative pathogen.

Recommended Dose and Dosage Adjustment

The recommended dosage of SIVEXTRO (tedizolid phosphate) is 200 mg administered once daily for six (6) days either orally as a tablet or as an intravenous (IV) infusion in patients ≥18 years of age.

Dosage and administration recommendations are summarized in Table 3.

Table 3 Dosage of SIVEXTRO

Infection	Route	Dosage	Frequency	Infusion Time	Duration of Treatment
Acute Bacterial Skin and Skin Structure Infection (ABSSSI)	IV	200 mg	Once daily	1 hour	6 days
	Oral	200 mg	Once daily	Not Applicable	

SIVEXTRO tablets may be taken with or without food.

Intravenous to oral switch may be instituted at the discretion of the physician, and no dose adjustment is necessary.

Dose Adjustments

Elderly: Based on safety and PK data, no dose adjustment is necessary in patients 65 years and older (see **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**, **Special Populations and Conditions**).

Hepatic impairment: Based on safety and pharmacokinetic data no dose adjustment is necessary for patients with mild or moderate hepatic impairment (Child Pugh score ≤7). Safety in patients with severe hepatic impairment (Child Pugh score ≥9) has not been established (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Special Populations and Conditions**).

Renal impairment: Based on safety and pharmacokinetic data no dose adjustment is required in patients with mild or moderate renal impairment (CrCL ≥30 mL/min). Safety in patients with severe (advanced) renal impairment (defined as CrCL <30 mL/min) including patients on dialysis, has not been established (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, **Special Populations and Conditions**).

Missed Dose
If a patient misses a dose, they should be advised to take it as soon as possible anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remain before the next dose, the missed dose should be skipped and the regular dosing schedule resumed. Doses should not be doubled.

Administration of Intravenous Infusion
SIVEXTRO is supplied as a sterile, lyophilized powder for injection in single-use vials of 200 mg. Each 200 mg vial must be reconstituted with 4 mL of Sterile Water for Injection and subsequently diluted only with 0.9% Sodium Chloride Injection, USP.

SIVEXTRO vials contain no antimicrobial preservatives and are intended for single use only.

Administer as an IV infusion only.

Do **not** mix SIVEXTRO with other drugs.

Reconstitution
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.

1. Reconstitute the SIVEXTRO vial with 4 mL of Sterile Water for Injection.
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 colourless to pale yellow in colour; the total storage time should not exceed 24 hours at either room temperature or under refrigeration at 2 to 8°C (36 to 46°F).
4. Tilt the upright vial and insert a syringe with appropriately sized needle into the bottom corner of the vial and remove 4 mL of the reconstituted solution. Do not invert the vial during extraction.
5. For administration, the reconstituted solution must be further diluted in 250 mL of 0.9% Sodium Chloride Injection, USP.
6. Slowly inject the 4 mL of reconstituted solution into a 250 mL bag of 0.9% Sodium Chloride Injection, USP. Invert the bag gently to mix. Do NOT shake the bag as this may cause foaming.

Administration
Administer as an intravenous infusion only.

Do not administer as an intravenous push or bolus.

Inspect the IV bag containing the reconstituted IV solution visually for particulate matter prior to administration. Discard if visible particles are observed.

The resulting solution is clear and colourless to pale yellow in colour. Discard if visible particles are observed. The total time from reconstitution to administration should not exceed 24 hours at room temperature or under refrigeration at 2 to 8°C (36 to 46°F). After reconstitution and dilution, SIVEXTRO should be administered over 1 hour.

Do not mix SIVEXTRO for injection with other drugs when administering. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal, or subcutaneous administration.

Compatible Intravenous Solutions
SIVEXTRO for injection is compatible with 0.9% Sodium Chloride Injection, USP.

Incompatibilities
SIVEXTRO for injection is incompatible with any solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Injection and Hartmann's Solution.

Limited data are available on the compatibility of SIVEXTRO with other IV drug substances, additives, or other medications and they should not be added to SIVEXTRO single use vials or infused simultaneously. If the same IV line is used for sequential infusion of several different drugs, the line should be flushed before and after infusion of SIVEXTRO with 0.9% Sodium Chloride Injection, USP.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In the event of overdosage, SIVEXTRO should be discontinued and general supportive treatment given. Hemodialysis does not result in meaningful removal of tedizolid from systemic circulation. The highest single dose administered in clinical trials was 1200 mg (6 tablets). At these supratherapeutic doses, no new safety signals emerged, but the incidence of common adverse events, including nausea, diarrhea, and headache were greater than observed with the therapeutic dose of 200 mg. All adverse events at this dose level were mild or moderate in severity.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Tedizolid phosphate is the prodrug of an oxazolidinone class antibiotic that is rapidly converted *in vivo* by phosphatases to the microbiologically active moiety tedizolid. It has been developed for both oral and intravenous use. Tedizolid binds to the peptidyl transferase of 50S ribosomal subunit and inhibits protein synthesis. Tedizolid is 4- to 32-fold more potent than the other drug

of oxazolidinone class. Results in *in vitro* time-kill studies show that tedizolid is bacteriostatic against staphylococci and streptococci.

Tedizolid is bacteriostatic *in vitro*; however, in the non-neutropenic mouse model, tedizolid has demonstrated bactericidal activity.

Pharmacodynamics

AUC/minimum inhibitory concentration (MIC) was shown to best correlate with efficacy in animal infection models.

Tedizolid phosphate has demonstrated *in vivo* activity in animal models of *S. aureus* (MRSA and MSSA) infection. In the neutropenic mouse thigh infection model of *S. aureus*, anti-staphylococcal killing was impacted. In granulocytopenic mice (neutrophil count <100 cells/mL), bacterial stasis was not achieved with a human-equivalent dose.

QT/QTc Prolongation: In a randomized, positive and placebo-controlled cross-over thorough QTc study, 48 enrolled subjects were administered a single oral dose of SIVEXTRO at therapeutic dose of 200 mg, SIVEXTRO at supratherapeutic dose of 1200 mg, placebo, and a positive control; no significant effects of SIVEXTRO on heart rate, electrocardiogram morphology, PR, QRS, or QT interval were detected. Therefore, SIVEXTRO has not demonstrated significant effect on cardiac repolarization.

Pharmacokinetics

Tedizolid phosphate is a prodrug that is rapidly converted by phosphatases to tedizolid, the microbiologically-active moiety following to oral and intravenous administration. Only the pharmacokinetic profile of tedizolid is discussed further due to negligible systemic exposure of tedizolid phosphate following to oral and intravenous administration.

Single dose pharmacokinetic parameters are predictive of multiple doses (see Table 4). Steady-state concentrations were achieved within 3 days in most subjects with tedizolid accumulation of approximately 30% as predicted by tedizolid half-life of approximately 12 hours.

Table 4 Mean (Standard Deviation) of Tedizolid Phosphate Pharmacokinetic Parameters Following Single and Multiple (Once-daily) Dose of 200 mg Once Daily Tedizolid Phosphate

	C_{max} (µg/mL)	T_{max} (h) [1]	AUC (µg·h/mL)[2]	CL or CL/F[3] (L/hr)
Oral				
Single Dose	2.0 (0.7)	2.5 (1.0 - 8.0)	23.8 (6.8)	6.9 (1.7)
Steady State	2.2 (0.6)	3.5 (1.0 – 6.0)	25.6 (8.4)	8.4 (2.1)
Intravenous				
Single Dose	2.3 (0.6)	1.1 (0.9 - 1.5)	26.6 (5.2)	6.4 (1.2)
Steady State	3.0 (0.7)	1.2 (0.9 - 1.5)	29.2 (6.2)	5.9 (1.4)

[1] Median (range)
[2] AUC is $AUC_{0-\infty}$ (AUC from time 0 to infinity) for single administration and AUC_{0-24} (AUC from time 0 to 24 hours) for multiple dose administrations
[3] CL = systemic clearance; CL/F = apparent oral clearance

Absorption: Peak plasma tedizolid concentrations were achieved within approximately 3 hours following oral administration of tedizolid phosphate under fasted conditions or at the end of 1 hour intravenous infusion of tedizolid phosphate. No dosage adjustment is required between oral or IV administration.

Total systemic exposure ($AUC_{0-\infty}$) was unchanged between fasted and fed (high-fat, high-calorie) conditions when administered as tedizolid phosphate di-sodium. Under fasted conditions, the pharmacokinetics of tedizolid was comparable when administered as tedizolid phosphate free acid or tedizolid phosphate di-sodium. SIVEXTRO (oral) may be administered with or without food.

Distribution: The protein binding of tedizolid to human plasma proteins was 70 to 90%. The mean steady state volume of distribution of tedizolid in healthy adults following a single IV dose of tedizolid phosphate 200 mg ranged from 67 to 80 L (approximately twice total body water). Steady-state concentrations, which were achieved within 3 days, indicate modest drug accumulation of approximately 30% following multiple once-daily oral or IV administrations. Tedizolid penetrated into the interstitial space fluid of adipose and skeletal muscle tissue with exposure similar to free drug exposure in plasma.

Metabolism: Tedizolid has been shown to be stable in rat, dog, monkey, and human liver microsomes *in vitro* and in animals, suggesting that transformation via Phase 1 hepatic oxidative metabolism is not a significant pathway for elimination. Other than tedizolid, which accounts for approximately 95% of the total radiocarbon AUC in plasma, there were no other significant circulating metabolites in humans. Eight metabolites were identified in plasma, urine, and feces. The only significant circulating metabolite found in plasma was the hydrolyzed alcohol product of tedizolid. The main metabolite found in feces and urine was a sulfate analog of tedizolid.

There was no degradation of tedizolid in human liver microsomes. Sulfation is the primary elimination pathway 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 (primarily as the sulfate conjugate of tedizolid) and 18% in urine, with most of the elimination (>85%) occurring within 96 hours. Less than 3% of tedizolid phosphate dose was excreted in feces and urine as unchanged tedizolid.

Special Populations and Conditions

Based on the population pharmacokinetic analysis, no demographic or clinical patient factors (including age, gender, race, ethnicity, weight, body mass index, markers of renal or liver function) that impact the pharmacokinetics of tedizolid were identified.

Hepatic Insufficiency: Following administration of a single 200 mg oral dose of SIVEXTRO the pharmacokinetics of tedizolid were not altered in subjects with moderate (n=8) or severe (n=8) hepatic impairment (Child-Pugh Class B and C, respectively).

Renal Insufficiency: Following administration of a single 200 mg IV dose of SIVEXTRO to 8 subjects with severe renal impairment defined as CrCL <30 mL/min, the C_{max} remained unchanged and $AUC_{0-\infty}$ was decreased by less than 10% compared to 8 matched healthy subject controls. Hemodialysis did not result in meaningful removal of tedizolid from systemic circulation, as assessed in subjects with end-stage renal disease (CrCL<15 mL/min).

STORAGE AND STABILITY

SIVEXTRO Tablets

Store at room temperature (15°C - 30°C).

SIVEXTRO for Injection

Store at room temperature (15°C - 30°C). Storage time of the reconstituted solution in the vial should not exceed 24 hours at either room temperature (15°C - 30°C) or under refrigeration at 2 to 8°C. The total time from reconstitution to administration of the diluted solution for infusion should not exceed 24 hour at room temperature or under refrigeration.

SIVEXTRO is incompatible with any diluent solutions containing divalent cations (e.g., Ca^{2+}, Mg^{2+}), including Lactated Ringer's Injection and Hartmann's Solution.

SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for SIVEXTRO tablets. For information on reconstitution for SIVEXTRO for injection, see **DOSAGE AND ADMINISTRATION** above.

DOSAGE FORMS, COMPOSITION AND PACKAGING

SIVEXTRO Tablets

SIVEXTRO Tablets are yellow film-coated and oval-shaped containing 200 mg of tedizolid phosphate; each tablet is debossed with "TZD" on one side and "200" on the other side.

SIVEXTRO Tablets contain the following inactive ingredients: crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol/macrogol, polyvinyl alcohol, povidone, talc, titanium dioxide, and yellow iron oxide.

Available pack sizes:

- 30 tablets in white 40 mL HDPE bottles with a child resistant closure
- Unit dose blister packs of 6 tablets

SIVEXTRO for Injection

SIVEXTRO Lyophilized Powder for Injection is a sterile white to off-white lyophilized powder for injection in a single-use clear glass vial containing 210 mg of tedizolid phosphate to allow delivery of 200 mg after reconstitution with 4 mL of Sterile Water for Injection. The inactive ingredients are mannitol and sodium hydroxide. May contain hydrochloric acid in minimal quantity for pH adjustment.

Supplied as a cartons containing 1 or 10 single-dose clear glass vials.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Tedizolid phosphate

Chemical name: (5R)-(3-{3-Fluoro-4-(6-(2-methyl-2H-tetrazol-5-yl)pyridin-3-yl)phenyl}-2-oxooxazolidin-5-yl)methyl dihydrogen phosphate

Molecular formula: $C_{17}H_{16}FN_6O_6P$

Molecular mass: 450.32

Structural formula:

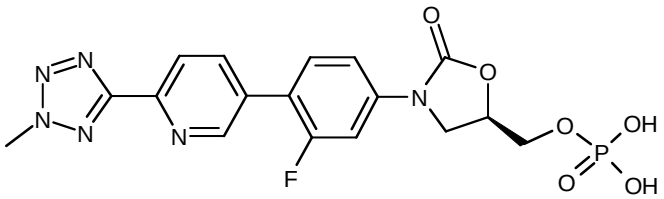

Table 5 Physicochemical Properties

Attribute	Description
Appearance	White to yellow solid
Aqueous Solubility (at 25°C)	
Water (pH 3.9) 0.1% Phosphoric Acid, pH 2.0 0.1 N HCl, pH 1.1 0.01 N HCl, pH 2.1 0.05 M Potassium Biphthalate, pH 4.0 0.05 M Potassium Phosphate, pH 6.0 0.05 M Sodium Phosphate, pH 8.0 0.1 M Potassium Borate, pH 9.0	0.1 mg/mL 0.003 mg/mL 0.005 mg/mL 0.005 mg/mL 0.5 mg/mL >195 mg/mL >200 mg/mL >200 mg/mL
Melting point	256.8°C
pKa	First pKa: 1.8 (calculated) Second pKa: 6.5 (measured by titration)
Partition Coefficient	-0.4
Optical Rotation (at 25°C, 1:1 H_2O:THF)	-48.3°

CLINICAL TRIALS

Study Demographics and Trial Design

A total of 1333 adults with acute bacterial skin and skin structure infections (ABSSSI) were randomized in two Phase 3 multicentre, double-blind, non-inferiority trials. Both trials compared SIVEXTRO™ (tedizolid phosphate) 200 mg once daily for 6 days *versus* linezolid 600 mg every 12 hours for 10 days. In trial 1, patients were treated with oral therapy, while in trial 2, patients could receive oral therapy after a minimum of 1 day of IV therapy at the investigator's discretion if 2 of 4 criteria were met: 1) no increase in primary lesion size from baseline; 2) temperature <37.7°C; 3) no worsening of local signs/symptoms since previous visit; and 4) improvement in at least 1 local sign/symptom since previous visit. Patients with cellulitis/erysipelas, major cutaneous abscess, or wound infection were enrolled in the studies. Patients with wound infections were allowed aztreonam and/or metronidazole as adjunctive therapy for gram-negative and/or anaerobic bacterial coverage, if needed. The intent-to-treat (ITT) patient population included all randomized patients.

In trial 1, 332 patients with ABSSSI were randomized to SIVEXTRO and 335 patients were randomized to linezolid. The majority (91%) of patients treated with SIVEXTRO in this trial were less than 65 years old. Patients treated with SIVEXTRO were predominantly White (84%), 13% had BMI ≥35 kg/m^2, 8% had diabetes mellitus, 35% were current or recent intravenous drug users, and 2% had moderate renal impairment (CrCL <60 mL/min). The overall median surface area of infection was 188 cm^2. The types of ABSSSI included were cellulitis/erysipelas (41%), wound infection (29%), and major cutaneous abscess (30%). In addition to local signs and symptoms of infection, patients were also required to have at least one regional or systemic sign of infection at baseline, defined as lymphadenopathy (87% of patients), temperature 38°C or higher (16% of patients), white blood cell count greater than 10,000 cells/mm^3 or less than 4000 cells/mm^3 (42%), or 10% or more band forms on white blood cell differential (4%).

In trial 2, 332 patients with ABSSSI were randomized to SIVEXTRO and 334 patients were randomized to linezolid. The majority (87%) of patients treated with SIVEXTRO in trial 2 were less than 65 years old. Patients treated with SIVEXTRO were predominantly White (86%), 16% had BMI ≥35 kg/m^2, 10% had diabetes mellitus, 20% were current or recent intravenous drug users, and 4% had moderate renal impairment (CrCL <60 mL/min). The overall median surface area of infection was 231 cm^2. The types of ABSSSI included were cellulitis/erysipelas (50%), wound infection (30%), and major cutaneous abscess (20%). In addition to local signs and symptoms of infection, patients were also required to have at least one regional or systemic sign of infection at baseline, defined as lymphadenopathy (71% of patients), temperature 38°C or higher (31% of patients), white blood cell count greater than 10,000 cells/mm^3 or less than 4000 cells/mm^3 (53%), or 10% or more band forms on white blood cell differential (16%).

Table 6 Summary of Demographics for the Two Phase 3 Trials in Patients with ABSSSI

Trial	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Gender (% M)
1	Noninferiority, global, multicentre, randomized, double-blind, double-dummy, active-controlled study in patients with ABSSSI	Oral 200 mg SIVEXTRO once daily for 6 days **Or** Oral 600 mg linezolid twice daily for 10 days	332 335	43.6 (18-86) 43.1 (18-100)	61 59
2	Noninferiority, global, multicentre, randomized, double-blind, double-dummy, active-controlled study in patients with ABSSSI	IV/oral* 200 mg SIVEXTRO once daily for 6 days **Or** IV/oral* 600 mg linezolid twice daily for 10 days	332 334	45.6 (17-86) 45.6 (15-89)	68 64

* An optional switch from IV to oral administration was allowed after at least 1 day of IV treatment at the investigator's discretion.

Study Results

The primary efficacy endpoint in trial 1 was early clinical response, defined as no increase from baseline lesion area at 48-72 hours after the first dose and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours in the ITT population.
The primary endpoint in trial 2 was early clinical response, defined as at least a 20% decrease from baseline lesion area at 48-72 hours after the first dose in the ITT population (see Table 7).

Table 7 Early Clinical Response in the ITT Patient Population

Trial Number	SIVEXTRO	Active Comparator	Treatment Difference (2-sided 95% CI)
No increase in lesion surface area from baseline and oral temperature of ≤37.6°C, confirmed by a second temperature measurement within 24 hours at 48-72 hours*			
Trial 1, N	332	335	
Responder, n (%)	264 (79.5)	266 (79.4)	0.1 (-6.1, 6.2)
Trial 2, N	332	334	
Responder, n (%)	286 (86.1)	281 (84.1)	2.0 (-3.5, 7.3)
At least a 20% decrease from baseline in lesion area at 48-72 hours**			
Trial 1, N	332	335	
Responder, n (%)	259 (78.0)	255 (76.1)	1.9 (-4.5, 8.3)
Trial 2, N	332	334	
Responder, n (%)	283 (85.2)	276 (82.6)	2.6 (-3.0, 8.2)

* Primary endpoint for trial 1; sensitivity analysis for trial 2
** Primary endpoint for trial 2; sensitivity analysis for trial 1

The protocol specified analyses included clinical response at the end of therapy (EOT) and Investigator-assessed clinical response at the post-therapy (PT) evaluation (7 - 14 days after the end of therapy) in the ITT patient population (Table 8). At the EOT and PT visits, clinical response was defined as resolution or near resolution of most disease-specific signs and symptoms, absence or near resolution of systemic signs of infection if present at baseline (lymphadenopathy, fever, >10% immature neutrophils, abnormal WBC count), and no new signs, symptoms, or complications attributable to the ABSSSI requiring further treatment of the primary lesion. Clinical evaluations at the PT visit were assessed by the investigator (Table 8).

Table 8 Clinical Response at End of Therapy and Investigator Assessed Clinical Response at Post-therapy Evaluation in ITT Patient Population from the Two Phase 3 ABSSSI Trials

	SIVEXTRO n/N (%)	Active Comparator n/N (%)	Treatment Difference** (2 sided 95% CI)
Clinical Response at End of Therapy*			
Trial 1	289/332 (87.0)	294/335 (87.8)	-0.8 (-5.8, 4.4)
Trial 2	289/332 (87.0)	294/334 (88.0)	-1.0 (-6.1, 4.1)
Trial 1 and Trial 2	578/664 (87.0)	588/669 (87.9)	-0.8 (-4.4 , 2.7)
Investigator Assessed Clinical Response at Post-therapy Evaluation			
Trial 1	284/332 (85.5)	288/335 (86.0)	-0.5 (-5.8, 4.9)
Trial 2	292/332 (88.0)	293/334 (87.7)	0.3 (-4.8, 5.3)
Trial 1 and Trial 2	576/664 (86.7)	581/669 (86.8)	-0.1 (-3.8, 3.6)

* Clinical response at EOT (Day 11 or 2 within days of last dose if not considered a clinical response) was determined as responders if patients were afebrile, had a decrease from baseline in size of primary ABSSSI lesion, had a clinical assessment of tenderness as mild or absent, had no purulent drainage, and took no other antibiotics.

** Treatment Difference=weighted responder rate for the SIVEXTRO treatment group minus linezolid for the controlled studies. 95% confidence interval is adjusted for study and calculated using the methodology of Miettinen and Nurminen.

Clinical response by baseline pathogens from the primary infection site or blood cultures for the microbiological intent-to-treat (MITT) patient population from the two Phase 3 ABSSSI studies are presented in Table 9 and Table 10.

Table 9 Early Clinical Response by Baseline Pathogen from the Two Phase 3 ABSSSI Trials (MITT Population)

Pathogen	No increase in lesion surface area from baseline and oral temperature of ≤37.6°C*		At least a 20% decrease from baseline in lesion area**	
	SIVEXTRO n/N (%)	Active Comparator n/N (%)	SIVEXTRO n/N (%)	Active Comparator n/N (%)
Staphylococcus aureus	276/329 (83.9)	278/342 (81.3)	280/329 (85.1)	276/342 (80.7)
Methicillin-resistant *S. aureus*	112/141 (79.4)	113/146 (77.4)	114/141 (80.9)	111/146 (76.0)
Methicillin-susceptible *S. aureus*	164/188 (87.2)	167/198 (84.3)	166/188 (88.3)	167/198 (84.3)
Streptococcus pyogenes	27/33 (81.8)	18/20 (90.0)	25/33 (75.8)	16/20 (80.0)
Streptococcus anginosus Group	22/30 (73.3)	26/28 (92.9)	22/30 (73.3)	25/28 (89.3)
Streptococcus agalactiae	6/9 (66.7)	8/10 (80.0)	6/9 (66.7)	7/10 (70.0)

Pooled analysis; n=number of patients in the specific category; N=Number of patients with the specific pathogen isolated from the ABSSSI

* Primary endpoint of trial 1

** Primary endpoint of trial 2

Table 10 Clinical Response at Post Therapy Evaluation by Baseline Pathogen from the Two Phase 3 ABSSSI Trials (MITT Population)

Pathogen	SIVEXTRO n/N (%)	Active Comparator n/N (%)
Staphylococcus aureus	291/329 (88.4)	303/342 (88.6)
Methicillin-resistant *S. aureus*	118/141 (83.7)	119/146 (81.5)
Methicillin-susceptible *S. aureus*	173/188 (92.0)	186/198 (93.9)
Streptococcus pyogenes	30/33 (90.9)	19/20 (95.0)
Streptococcus anginosus Group	21/30 (70.0)	25/28 (89.3)
Streptococcus agalactiae	8/9 (88.9)	8/10 (80.0)

Pooled analysis; n=number of patients in the specific category; N=Number of patients with the specific pathogen isolated from the ABSSSI
Baseline bacteremia in the tedizolid arm with relevant pathogens included two subjects with MRSA, four subjects with MSSA, two subjects with *S. pyogenes*, one subject with *S. agalactiae*, and one subject with *S. constellatus.* All of these subjects were Responders at the 48-72 hour evaluation. At the Post-therapy Evaluation (PTE), 8 of 10 subjects were considered clinical successes.

Results for all endpoints were consistent with the primary findings across other subgroups analyzed (including age, sex, and clinical syndrome as defined by cellulitis, abscess, or wound infection).

DETAILED PHARMACOLOGY

Animal Pharmacology

Primary Pharmacodynamics

In vitro and *in vivo* animal studies were conducted to evaluate the efficacy and safety profile of tedizolid. The intravenous and oral pharmacokinetic profiles of tedizolid phosphate are similar due to high (~70-91%) oral bioavailability.

In animals, the general pharmacological properties of tedizolid were investigated to evaluate its effects on major physiological systems.

Administration of tedizolid phosphate was effective against a variety of gram positive pathogens including methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*, streptococci and enterococci infections in systemic lethal and localized animal infection models of skin and soft tissue infections.

The *f*AUC/MIC ratio was the pharmacodynamic parameter shown to best correlate with efficacy in mouse thigh *S. aureus* infection models.

In the mouse thigh infection model of *S. aureus*, anti-staphylococcal 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.

Secondary Pharmacodynamics

Monoamine Oxidase (MAO) Inhibition

Tedizolid is a reversible inhibitor of MAO_A and MAO_B. MAO_A IC_{50} values were at concentrations approximately 5-fold above the free tedizolid human IV C_{max} value at the recommended dose of 200 mg.

The potential *in vivo* effects related to MAO inhibition were investigated in rodents. In rats, oral administration of tedizolid phosphate up to 150 mg/kg did not affect the pressor response to tyramine. Moreover, intraperitoneal administration of tedizolid phosphate to ICR mice at doses up to 300 mg/kg did not increase the occurrence of head twitches induced by injection of 5-HTP and did not increase brain monoamine levels. At the 300 mg/kg dose, plasma concentrations of tedizolid were approximately 28-fold greater than the clinical oral C_{max} value.

Safety Pharmacology

Central Nervous System Effects

Following oral administration of tedizolid phosphate (10, 30, and 100 mg/kg equivalent to 2.6, 8.6, and 33.0 times the human oral C_{max} at steady state) to mice, a slight (0.4 to 1.2°C) and transient decrease in body temperature (all doses), a transient (approximately 30%) decrease in locomotor activity (30 and 100 mg/kg), and a prolongation of hexobarbital sleep time (23.4% vs. vehicle control at 100 mg/kg) were observed.

Cardiovascular Effects

Both tedizolid and tedizolid phosphate were considered inactive in the hERG channel assay at concentrations up to 20.25 μM and 10 μM, respectively. These concentrations are approximately 12.5-fold greater than the free human steady state IV C_{max} at the recommended dose of 200 mg. Neither tedizolid nor tedizolid phosphate at concentrations up to 10 μM affected cardiovascular functioning of isolated rat hearts.

Oral administration of tedizolid phosphate to dogs at doses up to 200 mg/kg was not associated with any significant effect on blood pressure, heart rate, ECGs, or body temperature. An oral dose of 200 mg/kg is associated with a tedizolid plasma concentration 7-fold the oral human steady state C_{max} at the recommended dose of 200 mg.

Respiratory Effects

Oral administration of tedizolid phosphate (10, 30, and 100 mg/kg) to rats did not produce any significant respiratory changes. An oral dose of 100 mg/kg is associated with a tedizolid plasma concentration 14-fold the oral human steady state C_{max} at the recommended dose of 200 mg.

Renal System Effects

Oral administration of tedizolid phosphate (10, 30, and 100 mg/kg) to rats significantly increased urinary volume and decreased urinary sodium and chloride concentrations at the highest dose.

An oral dose of 100 mg/kg is associated with a tedizolid plasma concentration 14-fold the oral human steady state C_{max} at the recommended dose of 200 mg.

MICROBIOLOGY

Mechanism of Resistance

As a member of the oxazolidinone class of antibacterial agents, tedizolid is a bacterial protein synthesis inhibitor that interacts with the peptidyl transferase domain of 50S ribosomal subunit of the bacterial ribosome, thereby preventing translation from occurring by inhibiting formation of the initiation complex. Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to tedizolid. In the limited number of *Staphylococcus aureus* strains tested, the presence of the chloramphenicol-florfenicol resistance (*cfr*) gene did not result in resistance to tedizolid in the absence of chromosomal mutations.

Oxazolidinone class of antibacterial agents inhibit bacterial protein synthesis through a mechanism of action different from that of other antibacterial agents, including penicillins, cephalosporins, aminoglycosides, glycopeptides, lipopeptides, streptogramins, quinolones, macrolides, tetracyclines, and pleuromutilins. Therefore, tedizolid is active against pathogens that are resistant to these antibiotics. There is no known cross-resistance between tedizolid and other classes of antibiotics.

Frequency of Resistance

Spontaneous mutations conferring reduced susceptibility to tedizolid occur *in vitro* at a frequency rate of approximately 10^{-10}.

Interaction with Other Antimicrobials

In vitro drug combination studies with tedizolid and aztreonam, ceftriaxone, ceftazidime, imipenem, rifampin, trimethoprim/sulfamethoxazole, minocycline, clindamycin, ciprofloxacin, daptomycin, vancomycin, gentamicin, amphotericin B, ketoconazole, and terbinafine demonstrated neither synergy nor antagonism.

Spectrum of Activity

Tedizolid has been shown to be active against most isolates of the following bacteria, both *in vitro* and in clinical infections.

Aerobic and Facultative Gram-positive Microorganisms

- *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] strains)
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* Group (including *S. anginosus*, *S. intermedius*, and *S. constellatus*)

The following *in vitro* data are available, but their clinical significance has not been established. At least 90% of the following microorganisms exhibit an *in vitro* MIC less than or equal to the susceptible breakpoint for tedizolid. However, the safety and effectiveness of SIVEXTRO in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic and Facultative Anaerobic Gram-positive Microorganisms

- *Staphylococcus haemolyticus*
- *Staphylococcus lugdunensis*
- *Staphylococcus epidermidis*
- *Enterococcus faecalis* (vancomycin-susceptible and vancomycin-resistant strains)
- *Enterococcus faecium* (including vancomycin-susceptible and vancomycin-resistant strains)
- *Peptostreptococcus* spp. (including *P. anerobius* and *P. micros*)

Susceptibility Test Methods
When available, the clinical microbiology laboratory should provide cumulative results of the *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial drug product for treatment.

Dilution Techniques
Quantitative methods are used to determine MICs. These MIC values provide estimates of the susceptibility of bacteria to antimicrobial compounds. The MIC values should be determined using a standardized procedure based on dilution methods (broth, agar, or microdilution) or equivalent using standardized inoculum and concentrations of tedizolid. The MIC values should be interpreted according to the criteria provided in Table 11.

Table 11 Susceptibility Interpretive Criteria for SIVEXTRO

Pathogen	Minimum Inhibitory Concentrations (µg/mL)	
	S	R
Staphylococcus aureus (methicillin-resistant and methicillin-susceptible strains)	≤0.5	≥1
Streptococcus pyogenes	≤0.5	≥1
Streptococcus agalactiae	≤0.5	≥1
Streptococcus anginosus Group*	≤0.25	≥0.5

S=susceptible, R=resistant
*Includes *S. anginosus*, *S. intermedius*, *S. constellatus*

Quality Control
Standardized susceptibility test procedures require the use of laboratory control microorganisms to monitor and ensure the accuracy and precision of supplies and reagents used in the assay, and the techniques of the individuals performing the test. Tedizolid should provide the following range of MIC values noted in Table 12.

Table 12 Acceptable Quality Control Ranges for Susceptibility Testing

Quality Control Organism	Minimum Inhibitory Concentrations (µg/mL)
Staphylococcus aureus ATCC 29213	0.25 - 1
Staphylococcus aureus ATCC 25923	Not Applicable
Streptococcus pneumoniae ATCC 49619	0.12 - 0.5

TOXICOLOGY

Single-dose toxicity, repeat-dose toxicity, genotoxicity, and reproductive toxicity studies were conducted to investigate the toxicity of tedizolid. The key findings from these studies are briefly summarized below.

General Toxicology
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. No adverse effects were noted in dogs following repeated-oral or intravenous administration at doses associated with tedizolid exposure levels (AUC) ≥3-fold greater than the plasma exposure associated with the human therapeutic dose.

Tedizolid phophate was administered orally once-daily to pigmented Long Evans rats for up to 9 months. 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.

Genotoxicity
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 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.

Carcinogenicity

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

Reproduction and Development Toxicology

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_{0-24} 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.

In a pre-postnatal study, there were no adverse maternal or offspring effects when female rats were treated during pregnancy and lactation with tedizolid phosphate at the highest tested dose of 3.75 mg/kg/day, with plasma tedizolid exposure (AUC) approximately equivalent to the human plasma AUC exposure at the clinical therapeutic dose of 200 mg/day.

Immunotoxicity

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.

Phototoxicity

No ocular observations, skin reactions, or related histopathological findings were identified at acute oral dosages of tedizolid phosphate up to 60 mg/kg in female pigmented rats using a validated model of phototoxicity. The absence of phototoxicity observed in the chronic neuropathology study in pigmented rats, particularly in ocular structures, supports lack of toxicity to pigmented structures.

REFERENCES

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2. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing – 23rd Informational Supplement. CLSI document M100 S23 (ISBN 1-56238-865-7 [Print]; ISBN 1-56238-866-5 [Electronic]). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2013.

PART III: CONSUMER INFORMATION

[Pr]SIVEXTRO™

tedizolid phosphate tablets
tedizolid phosphate for injection

This leaflet is Part III of a three-part "Product Monograph" published when SIVEXTRO was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about SIVEXTRO. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
SIVEXTRO is a medicine which is used to treat infections of the skin caused by certain bacteria, in adults 18 years of age and over.

What it does:
SIVEXTRO belongs to a class of medicines called antibiotics and it works by stopping protein synthesis in certain bacteria, reducing bacterial growth and the number of bacteria, thereby reducing the skin infection.

When it should not be used:
- If you are allergic to the active substance in SIVEXTRO or any of the other ingredients in this medicine (see *What the important non-medicinal ingredients are*)

What the medicinal ingredient is:
Tedizolid phosphate

What the important nonmedicinal ingredients are:
SIVEXTRO tablets contain: crospovidone, magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol/macrogol, polyvinyl alcohol, povidone, talc, titanium dioxide, and yellow iron oxide.

SIVEXTRO for injection contains: mannitol and sodium hydroxide. May contain hydrochloric acid in minimal quantity for pH adjustment.

What dosage forms it comes in:
200 mg tedizolid phosphate tablets
Vial containing 200 mg tedizolid phosphate for injection, provided as a powder that will be dissolved in sterile water and diluted with salt water so that it can be injected.

WARNINGS AND PRECAUTIONS

Antibacterial drugs including SIVEXTRO should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold).

Do not drive or use machines if you feel dizzy, sleepy, or tired after taking SIVEXTRO.

BEFORE you use SIVEXTRO talk to your doctor or pharmacist if:
- You are allergic to this drug or any of the ingredients in SIVEXTRO or components of the container
- You have neutropenia (low white blood cells)
- You are pregnant or plan to become pregnant. If you are of child-bearing potential, you should use reliable contraception during SIVEXTRO use.
- You are breastfeeding or plan to breastfeed. You should not breastfeed while taking SIVEXTRO.

INTERACTIONS WITH THIS MEDICATION

Clinical drug interaction studies have not been done with SIVEXTRO.
Tell your doctor if you are using any of the following drugs as they may interact with SIVEXTRO:

- anticancer drugs (e.g., imatinib, lapatinib)
- anticoagulants (e.g., warfarin)
- antipsychotic drugs (e.g., midazolam, triazolam, pimozide)
- cholesterol lowering drugs (e.g., atorvastatin, fluvastatin, lovastatin, rosuvastatin)
- heart drugs (e.g., quinidine, digoxin)
- high blood pressure medications (e.g., olmesartan, valsartan)
- immune suppressants (e.g., cyclosporine, tacrolimus, sirolimus)
- medications to control blood sugar (e.g., glyburide, repaglinide)
- oral contraceptives
- opioid analgesics (e.g., alfentanil, fentanyl)
- selective serotinin re-uptake inhibitors (SSRI's)
- serotonin norepinephrine re-uptake inhibitors (SNRI's)

PROPER USE OF THIS MEDICATION

Usual adult dose:
200 mg taken once a day as a tablet or as an intravenous infusion over 1 hour, as decided by your doctor.
Treatment usually lasts for 6 days.
SIVEXTRO may be taken with or without food.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss a dose of SIVEXTRO, you should take the dose as soon as possible, anytime up to 8 hours before the next scheduled dose. This will help keep a constant amount of medication in your blood. If less than 8 hours remains before the next dose, skip the missed dose and go back to the regular dosing schedule. Do not take double doses.

You should always take the full number of doses prescribed by your doctor because not completing the full course of therapy may decrease the effectiveness of treatment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, SIVEXTRO can cause side effects although not everyone experiences them. Most of side effects are mild and do not mean that you have to stop taking the medicine.

If you experience symptoms such as severe diarrhea (bloody or watery) with or without fever, abdominal pain, or tenderness, you may have *Clostridium difficile* colitis (bowel inflammation). If this occurs, stop taking SIVEXTRO and contact your healthcare professional immediately.

Common side effects (affecting 1-10 users in 100):

- Nausea
- Headache
- Diarrhea
- Vomiting
- General itching
- Dizziness
- Tiredness

If any of these side effects bother you or become serious, please tell your doctor.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Uncommon	Severe allergic reaction such as hives, itching or rash, swelling of tissues (such as mouth, throat, lips, hands), difficulty breathing			√
	Frequent watery and/or bloody diarrhea with or without stomach cramps		√	
Common	Vomiting	√		

This is not a complete list of side effects. For any unexpected effects while taking SIVEXTRO, contact your doctor or pharmacist.

HOW TO STORE IT

Keep out of the reach and sight of children.

SIVEXTRO Tablets:
Store at room temperature (15°C - 30°C). Do not use this medication after the expiration date printed on the label.

SIVEXTRO for Injection:
The healthcare professional will store the product at room temperature (15°C - 30°C). Storage time of the reconstituted solution in the vial should not exceed 24 hours at either room temperature (15°C - 30°C) or under refrigeration at 2 to 8°C. The total time from reconstitution to administration of the diluted solution for infusion should not exceed 24 hour at room temperature or under refrigeration.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701D
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about SIVEXTRO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website or Merck Canada web site www.merck.ca or by calling Merck Canada at 1-800-567-2594.

To report an adverse event related to SIVEXTRO, please contact 1-800-567-2594.

This leaflet was prepared by Merck Canada

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