Applicant: MSD (Pty) Ltd
APPROVED PROFESSIONAL INFORMATION
SIVEXTRO 200 mg Tablet and 200 mg Powder for Solution for Infusion

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

SIVEXTRO® 200 mg Tablet

SIVEXTRO® 200 mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

SIVEXTRO Tablet: Each film-coated tablet contains 200 mg tedizolid phosphate.

SIVEXTRO Powder for Solution for Infusion: Each vial contains disodium tedizolid phosphate corresponding to 200 mg tedizolid phosphate.

After reconstitution each mL contains 50 mg tedizolid phosphate.

Contains sugar (mannitol). Each tablet contains 78 mg mannitol and each vial contains 100 mg mannitol per dose.

3 PHARMACEUTICAL FORM

SIVEXTRO Film-coated Tablet: SIVEXTRO Tablets are oval (13,8 mm long by 7,4 mm wide) yellow film-coated tablets containing 200 mg of tedizolid phosphate; each tablet is debossed with “TZD” on one side and “200” on the other side.

SIVEXTRO for Intravenous Infusion: SIVEXTRO for Intravenous Infusion is supplied in single use vials containing 200 mg tedizolid phosphate as a sterile, lyophilised powder.

Reconstituted SIVEXTRO: A clear colourless or light-yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SIVEXTRO is indicated for the treatment of the infections listed below.

Acute bacterial skin and skin structure infections (ABSSSI) also known as complicated skin and soft tissue infections (cSSTI) or complicated skin-and skin structure infections (cSSSI), caused by susceptible isolates of the following gram-positive microorganisms, in adults (18 years of age or older):

- *Staphylococcus aureus*, including:
  - methicillin-resistant [MRSA] and
  - methicillin-susceptible [MSSA] isolates,
- *Streptococcus pyogenes,*
- *Streptococcus agalactiae*,
- *Streptococcus anginosus* Group, including
  - *Streptococcus anginosus*,
  - *Streptococcus intermedius,* and
  - *Streptococcus constellatus*, and
- *Enterococcus faecalis*

To reduce the development of drug-resistant bacteria and maintain the effectiveness of SIVEXTRO prescribers should adhere to the principles of antibiotic stewardship.

4.2 Posology and method of administration

Posology

Acute Bacterial Skin and Skin Structure Infections

The recommended dosage and administration is described in Table 1.

Table 1: Dosage of SIVEXTRO

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

*Treatment durations longer than 6 days are not required in patients with ABSSSI

May be taken with or without food or drink.

Intravenous and oral formulations may be used interchangeably, and no dose adjustment is necessary.

If patients miss a dose, they should take it as soon as possible anytime up to 8 hours prior to their next scheduled dose. If less than 8 hours remain before the next dose, wait until their next scheduled dose.

Method of administration

For instructions on dilution of the product before administration, see section 6.6.

Administration of SIVEXTRO Powder for Solution for Infusion

Administer as an intravenous infusion only.

Do not administer as an intravenous push or bolus. Do not mix SIVEXTRO with other drugs when administering. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal or subcutaneous administration.

The intravenous bag containing the reconstituted and diluted intravenous solution should be inspected visually for particulate matter prior to administration. Discard if visible particles are observed. The resulting solution is clear and colourless to pale-yellow in colour.

After reconstitution and dilution, SIVEXTRO is to be administered via intravenous infusion using a total time of 1 hour.

The total time from reconstitution to administration should not exceed 24 hours at room temperature or under refrigeration at 2 °C to 8 °C.

Special populations

Renal Impairment

No dosage adjustment of SIVEXTRO is required.

Hepatic impairment

No dosage adjustment of SIVEXTRO is required.

Elderly (≥ 65 years of age)

No adjustment of SIVEXTRO dosage is necessary for elderly patients (see **Specific Populations, Geriatric**). The clinical experience in patients ≥ 75 years is limited.

Gender

No dosage adjustment of SIVEXTRO is required.

Obesity/BMI

No dosage adjustment of SIVEXTRO is required based on Body Mass Index (BMI).

Race

No dosage adjustment of SIVEXTRO is required based on race.

Paediatric population

Safety and effectiveness of SIVEXTRO in patients under the age of 18 years have not been established.

4.3 Contraindications

SIVEXTRO is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients listed in 6.1 List of excipients.

4.4 Special warnings and precautions for use

Patients with neutropenia

The safety and efficacy of tedizolid phosphate in patients with neutropenia (neutrophil counts < 1 000 cells/mm^3) 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

Decreased platelets, decreased haemoglobin and decreased neutrophils have been observed in a few subjects during treatment with tedizolid phosphate. In cases where tedizolid phosphate was discontinued, the affected haematological parameters have returned back to pre-treatment levels. Myelosuppression (including anaemia, leukopenia, pancytopenia and thrombocytopenia) has 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. Thrombocytopenia has been reported in patients treated with tedizolid phosphate in post-marketing experience. Most cases of thrombocytopenia occurred with treatment lasting longer than the recommended duration.

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 SIVEXTRO (see section 4.8). CDAD may range in severity from mild diarrhoea to fatal colitis. Treatment with SIVEXTRO alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

CDAD must be considered in all patients who present with diarrhoea during and following SIVEXTRO use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines.

If CDAD is suspected or confirmed, SIVEXTRO should be discontinued, if possible. 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 an inhibitor of monoamine oxidase (MAO) *in vitro* (see section 4.5).

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 (see section 4.5).

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 micro-organisms

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.

4.5 Interaction with other medicines and other forms of interaction

Effects of other medicines on SIVEXTRO

In vitro studies have shown that drug interactions between tedizolid and inhibitors or inducers of cytochrome P450 (CYP) isoenzymes are unanticipated. Transformation via Phase 1 hepatic oxidative metabolism is not a significant pathway for elimination of SIVEXTRO.

Multiple sulfotransferase (SULT) isoforms (SULT1A1, SULT1A2 and SULT2A1) were identified *in vitro* that are capable of conjugating tedizolid which suggests that no single isozyme is critical to the clearance of tedizolid.

Effects of SIVEXTRO on other medicines

Drug Metabolising Enzymes

Neither SIVEXTRO nor the active metabolite, tedizolid, detectably inhibited or induced the metabolism of selected CYP enzyme substrates. These results suggest that drug-drug interactions based on oxidative metabolism are unlikely.

A clinical study comparing the single dose (2 mg) pharmacokinetics of midazolam (CYP3A4 substrate) alone or in combination with SIVEXTRO (once daily 200 mg oral dose for 10 days), demonstrated no clinically meaningful difference in midazolam C_{max} or AUC.

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 Breast Cancer Resistance Protein [BCRP]) was tested *in vitro*. No clinically relevant interactions are expected to occur with these transporters, with the exception of BCRP.

A clinical study comparing the single dose (10 mg) pharmacokinetics of rosuvastatin (BCRP substrate) alone or in combination with SIVEXTRO increased the rosuvastatin AUC and C_{max}, by approximately 70 % and 55 %, respectively, when co-administered with

SIVEXTRO. Orally administered SIVEXTRO can result in inhibition of BCRP at the intestinal level, increasing plasma concentrations of BCRP substrates, and the potential for adverse reactions. If possible, an interruption in the treatment of the co-administered BCRP substrate medicinal product should be considered during the 6 days of treatment with SIVEXTRO, especially for BCRP substrates with a narrow therapeutic index (e.g. methotrexate, topotecan or rosuvastatin).

Monoamine Oxidase Inhibition

Tedizolid is an inhibitor of monoamine oxidase (MAO) *in vitro*. The interaction with MAO inhibitors could not be evaluated in Phase 2 and 3 trials, as subjects taking such medications were excluded from the trials.

Adrenergic Agents

Two placebo-controlled crossover studies were conducted to assess the potential of 200 mg oral SIVEXTRO 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 SIVEXTRO compared to 425 mg with placebo.

Potential Serotonergic Interactions

SIVEXTRO at doses of up to 30-fold above human equivalent did not increase serotonergic response in 5-HTP mouse head twitch model from vehicle control. Due to the choice of comparator, patients taking serotonergic medicines could not be enrolled in the clinical trials.

Use with Tyramine-Rich Foods

No restrictions are required on tyramine-rich food.

4.6 Fertility, pregnancy and lactation

Pregnancy

The use of SIVEXTRO during pregnancy is not recommended.

There are no adequate and well-controlled studies of SIVEXTRO in pregnant women.

Embryo-foetal development studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4-fold and 6-fold, respectively, those expected in humans. In embryo-foetal studies, SIVEXTRO was shown to produce foetal developmental toxicities in mice and rats. Foetal developmental effects occurring in mice in the absence of maternal toxicity included reduced foetal weights and an increased incidence of costal cartilage fusion at the high dose of 25 mg/kg/day (4-fold the estimated human exposure level based on AUCs). In rats, decreased foetal weights and increased skeletal variations including reduced ossification of the sternabrae, vertebrae, and skull were observed at the high dose of 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 foetal toxicity in mice (5 mg/kg/day) as well as maternal and foetal 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 dose of 200 mg/day.

Impairment of 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.

Breastfeeding

Mothers should not use SIVEXTRO while breastfeeding their babies.

Tedizolid is excreted in the breast milk of rats. A risk to the breastfed infant cannot be excluded.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. SIVEXTRO may cause dizziness, fatigue or, uncommonly, somnolence which could affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

Adults

The most frequently reported adverse reactions occurring in patients receiving tedizolid phosphate in the pooled controlled Phase 3 clinical studies (tedizolid phosphate 200 mg once daily for 6 days) werenausea (6,9 %), headache (3,5 %), diarrhoea (3,2 %) and vomiting (2,3 %), and were generally mild to moderate in severity.

The safety profile was similar when comparing patients receiving intravenous tedizolid phosphatealone to patients who received oral administration alone, except for a higher reported rate of gastrointestinal disorders associated with oral administration.

Paediatric population

The safety of tedizolid phosphate was evaluated in one Phase 3 clinical trial, which included 91 paediatric patients (12 to <18 years of age) with ABSSSI treated with IV and/or oral SIVEXTRO 200 mg for 6 days and 29 patients treated with comparator agents for 10 days.

Tabulated list of adverse reactions

The following adverse reactions have been identified in two comparative pivotal Phase 3 studies in adults treated with SIVEXTRO (Table 2). Increased ALT, increased AST and liver function tests abnormal were the only adverse drug reactions reported in one comparative Phase 3 study in patients12 to < 18 years of age. Adverse reactions are classified by preferred term and System Organ Class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Table 2 Adverse reactions by body system and frequency reported in clinical trials and/or post-marketing use

System Organ Class	Frequency	Adverse reactions

Infections and infestations	Uncommon	Vulvovaginal mycotic infection, fungal infection, vulvovaginal candidiasis, abscess, *Clostridioides difficile* colitis, dermatophytosis, oral candidiasis, respiratory tract infection
Blood and lymphatic system disorders	Uncommon	Lymphadenopathy
	Not known*	Thrombocytopenia*
Immune system disorders	Uncommon	Drug hypersensitivity
Metabolism and nutrition disorders	Uncommon	Dehydration, diabetes mellitus inadequate control, hyperkalaemia
Psychiatric disorders	Uncommon	Insomnia, sleep disorder, anxiety, nightmare
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Somnolence, dysgeusia, tremor, paraesthesia, hypoaesthesia
Eye disorders	Uncommon	Vision blurred, vitreous floaters
Cardiac disorders	Uncommon	Bradycardia
Vascular disorders	Uncommon	Flushing, hot flush

Respiratory, thoracic and mediastinal disorders	Uncommon	Cough, nasal dryness, pulmonary congestion
Gastrointestinal disorders	Common	Nausea, diarrhoea, vomiting
	Uncommon	Abdominal pain, constipation, abdominal discomfort, dry mouth, dyspepsia, abdominal pain upper, flatulence, gastroesophageal reflux disease, haematochezia, retching
Skin and subcutaneous tissue disorders	Common	Pruritus generalised
	Uncommon	Hyperhidrosis, pruritus, rash, urticaria, alopecia, rash erythematous, rash generalised, acne, pruritus allergic, rash maculo-papular, rash papular, rash pruritic
Musculoskeletal and connective tissue disorders	Uncommon	Arthralgia, muscle spasms, back pain, limb discomfort, neck pain
Renal and urinary disorders	Uncommon	Urine odour abnormal

Reproductive system and breast disorders	Uncommon	Vulvovaginal pruritus
General disorders and administration site conditions	Common	Fatigue
	Uncommon	Chills, irritability, pyrexia, peripheral oedema
Investigations	Uncommon	Grip strength decreased, transaminases increased, white blood cell count decreased

*Based on post-marketing reports. Since these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which istherefore categorised as not known.

Post-marketing Experience

The following adverse drug reaction, not listed above, has been reported during worldwide post-marketing experience:

Blood and Lymphatic System Disorders

Thrombocytopenia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

A.20.1.1 Broad and medium spectrum antibiotics

5.1 Pharmacodynamic properties

Tedizolid phosphate is a prodrug that is converted in the body to the biologically active moiety, tedizolid an oxazolidinone antibacterial agent.

Tedizolid is primarily active against Gram-positive bacteria.

Microbiology

The results of *in vitro* time-kill studies show that tedizolid is bacteriostatic against enterococci, staphylococci and streptococci.

Mechanisms of 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 (G2576T and T2500A). Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to tedizolid.

A second resistance mechanism is encoded by a plasmid-borne and transposon associated chloramphenicol-florfenicol resistance (*cfr*) gene, conferring resistance in staphylococci and enterococci to oxazolidinones, phenicols, lincosamides, pleuromutilins, streptogramin A and 16-membered macrolides. Due to a hydroxymethyl group in the C5 position, tedizolid retains significant activity against strains of *Staphylococcus aureus* that express the *cfr* gene in the absence of chromosomal mutations.

Resistance Development

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

In experiments to evaluate the resistance development during serial passage, tedizolid displayed an increase of MIC of 0- and 8-fold against *S. aureus* ATCC 29213 (MSSA) and *S. aureus* ATCC 33591 (MRSA) respectively.

Interactions with Other Antimicrobials

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

Antibacterial activity against other relevant pathogens

Clinical efficacy has not been established against the following pathogens:

Aerobic and Facultative Anaerobic Gram-positive Microorganisms

- *Staphylococcus epidermidis* (including methicillin-susceptible and methicillin-resistant strains)
- *Enterococcus faecalis* (vancomycin-resistant strains)
- *Enterococcus faecium* (including vancomycin-susceptible and vancomycin-resistant strains)

The following Gram-negative species are not susceptible to tedizolid:

- *Acinetobacter baumanii*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

PK/PD Relationship

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 2 000 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 SIVEXTRO for the treatment of neutropenic patients (neutrophil counts <1 000 cells/mm^3) have not been evaluated.

Cardiac Electrophysiology

In a randomised, 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 1 200 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 does not affect cardiac repolarisation.

5.2 Pharmacokinetic Properties

General Introduction

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 Table 3.

Table 3: Mean (Standard Deviation) Steady-State Pharmacokinetic Parameters of Tedizolid following Single and Multiple (Once-daily) Dose Administration of 200 mg Oral or Intravenous Tedizolid Phosphate

Pharmacokinetic Parameters of Tedizolid*	Oral Tablet		IV	
	Single Dose N=16	Steady-State N=18	Single Dose N=9	Steady-State N=9

C_{max} (µg/mL)	2,0 (0,7)	2,2 (0,6)	2,3 (0,6)	3,0 (0,7)
T_{max} (h)†	2,5 (1,0 to 8,0)	3,5 (1,0 to 6,0)	1,1 (0,9 to 1,5)	1,2 (0,9 to 1,5)
AUC (µg·h/mL)‡	23,8 (6,8)	25,6 (8,5)	26,6 (5,2)	29,2 (6,2)
CL or CL/F (L/hr)	7,5 (2,3)	6,9 (1,7)	6,4 (1,2)	5,9 (1,4)

*C_{max}, maximum concentration; T_{max}, time of C_{max}; AUC, area under the concentration-time curve; CL, systemic clearance; CL/F, apparent oral clearance; IV, intravenous

†Median (range)

‡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 administration

No major pharmacokinetic differences were observed in Latinos and Asians

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 following a single oral dose of ^{14}C-labelled tedizolid.

There was no degradation of tedizolid in human liver microsomes indicating tedizolid is unlikely to be a substrate for hepatic CYP450 enzymes.

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

Elimination

Tedizolid is eliminated in excreta, primarily as a non-circulating and microbiologically inactive sulphate conjugate.

Following single oral administration of ^{14}C-labelled SIVEXTRO under fasted conditions, the majority of elimination occurred via the liver with 81,5 % of the radioactive dose recovered in faeces and 18 % in urine, with most of the elimination (> 85 %) occurring within 96 hours. Less than 3 % of SIVEXTRO administered dose is excreted as active tedizolid. The elimination half-life of tedizolid is approximately 12 hours and the intravenous clearance is 6 to 7 L/h.

Special populations

Based on the population pharmacokinetic analysis, there is no clinically relevant demographic or clinical patient factor (which included age, gender, race, ethnicity, weight, body mass index and measures of renal or liver function) which affects the pharmacokinetics of tedizolid.

Renal Insufficiency

Following administration of a single 200 mg IV dose of SIVEXTRO to 8 subjects with severe renal impairment defined as eGFR < 30 mL/min/1,73 m^2, the C_{max} was basically unchanged and $AUC_{0-\infty}$ was changed by < 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/1,73 m^2). No dosage adjustment is necessary in patients with severe renal impairment or patients on haemodialysis.

Hepatic Insufficiency

Following administration of a single 200 mg oral dose of SIVEXTRO, no clinically meaningful changes in mean tedizolid C_{max} and $AUC_{0-\infty}$ were observed in patients with moderate (n=8)

or severe (n=8) hepatic impairment (Child-Pugh Class B and C) compared to 8 matched healthy control subjects. No dose adjustment is necessary for patients with hepatic impairment.

Paediatric patients

The safety and efficacy of SIVEXTRO in children aged from birth to < 18 years have not yet been established.

Adolescents

The pharmacokinetic property of tedizolid was evaluated in adolescent subjects (ages 12 to 17; n=20) following administration of a single oral or IV dose of SIVEXTRO 200 mg. The mean C_{max} and $AUC_{0-\infty}$ for oral or IV administration of tedizolid 200 mg were similar in adolescent and in healthy adult subjects. No dosage adjustment is necessary based on age.

Elderly

The pharmacokinetic property of tedizolid was evaluated in a Phase 1 study conducted in elderly healthy volunteers (age 65 years and older, with at least 5 subjects at least 75 years old; n=14) compared to younger control subjects (25 to 45 years old; n=14) following administration of a single oral dose of SIVEXTRO 200 mg. No dosage adjustment of SIVEXTRO is necessary in elderly patients.

Gender

The impact of gender on the pharmacokinetics of SIVEXTRO was evaluated in healthy males and females clinical trials and in a population pharmacokinetics analysis. The

pharmacokinetics of tedizolid is comparable in males and females. No dosage adjustment of SIVEXTRO is necessary based on gender.

Obesity

The impact of obesity, as measured by body mass index (BMI ≥ 30) on the pharmacokinetics of SIVEXTRO was evaluated in a population pharmacokinetics analysis of clinical trial data. Exposures in subjects with BMI values < 30, 30 to 35 or > 35 were similar. No dosage adjustment of SIVEXTRO is necessary based on BMI.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

SIVEXTRO 200 mg Tablet:

Tablet core: microcrystalline cellulose, mannitol (78 mg), povidone, crospovidone and magnesium stearate.

Film coat: polyvinyl alcohol, titanium dioxide (E171), macrogol, talc and yellow iron oxide (E172).

SIVEXTRO 200 mg Powder for Solution for Infusion: mannitol (100 mg), sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment).

6.2 Incompatibilities

DO NOT USE SIVEXTRO with any solutions containing divalent cations (e.g. Ca^{2+}, Mg^{2+}). SIVEXTRO is not compatible with such solutions, including Lactated Ringer's Injection and Hartmann's Solution.

Do not mix or co-infuse SIVEXTRO with other medications, as there are limited data on the compatibility with other intravenous substances, additives, or medications. 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 solution.

Compatible Intravenous Solutions and Other Medicinal Products

SIVEXTRO is compatible with 0,9 % Sodium Chloride solution.

6.3 Shelf life

SIVEXTRO Tablets: 36 months when stored below 30 °C when tedizolid phosphate film-coated tablets are packaged in polyvinyl chloride (PVC)/polyvinylidene chloride (PVDC) foil blisters.

SIVEXTRO Powder for Solution for Infusion: 36 months when packaged in 10 mL Ph. Eur. Type I glass vials with a 20 mm neck finish, a 20 mm grey chlorobutyl rubber stopper and a 20 mm aluminium seal with a polypropylene flip-off top.

6.4 Special precautions for storage

SIVEXTRO Tablets and SIVEXTRO Powder for Solution for Infusion should be stored at 20 °C to 25 °C.

Reconstituted SIVEXTRO: The total time from reconstitution to the start of administration should not exceed 24 hours at either room temperature or under refrigeration at 2 °C to 8 °C after reconstituted product is added to 250 mL compatible IV solution.

6.5 Nature and contents of container

SIVEXTRO Tablets are supplied in blister packs of 6 tablets. 6 x 1 tablet in aluminium/Polyethylene Terephthalate (PET)/Paper foil and polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) clear film perforated child-resistant unit-dose blisters.

SIVEXTRO Powder for Solution for Infusion is supplied as a sterile lyophilised powder for injection in single-use Type I (10 mL) clear borosilicate tubing glass vial with a siliconized grey chlorobutyl rubber stopper, each containing 210 mg tedizolid phosphate to allow delivery of 200 mg after reconstitution with 4 mL of Sterile Water for Injection.
Available in packs of 1 vial and 6 vials.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

SIVEXTRO Powder for Solution for Infusion

Administer as an intravenous infusion only.

Do not administer as an intravenous push or bolus. Do not mix SIVEXTRO with other drugs when administering. It is not intended for intra-arterial, intramuscular, intrathecal, intraperitoneal or subcutaneous administration.

SIVEXTRO is supplied as a sterile lyophilised powder for injection in single-use vials, of 200 mg. Each vial must be reconstituted with Sterile Water for Injection and subsequently diluted only with 0,9 % Sodium Chloride Injection. Note: To minimise foaming, AVOID vigorous agitation or shaking of the vial during or after reconstitution.
The contents of the vial should be reconstituted using aseptic technique as follows:

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 room temperature or under refrigeration at 2 °C to 8 °C (36 °F 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 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. Slowly inject the 4 mL of reconstituted solution into a 250 mL bag of 0,9 % Sodium Chloride Injection. Invert the bag gently to mix. Do NOT shake the bag as this may cause foaming.

No preservative or bacteriostatic agent is present in SIVEXTRO.

7 HOLDER OF CERTIFICATE OF REGISTRATION

MSD (Pty) Ltd

117 16th Road

Halfway House

1685

South Africa

8 REGISTRATION NUMBERS

SIVEXTRO 200 mg Tablets: 52/20.1.1/0158

SIVEXTRO 200 mg Powder for Solution for Infusion: 52/20.1.1/0159

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 June 2021

10 DATE OF REVISION OF THE TEXT

30 July 2024