SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Sivextro® 200 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg tedizolid phosphate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Oval (13.8 mm long by 7.4 mm wide) yellow film-coated tablet debossed with "TZD" on the obverse side and "200" on the reverse side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sivextro tablets are indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in:

adults

adolescents and children weighing at least 35 kg.

See sections 4.4 and 5.1.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

Tedizolid phosphate tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral presentation when clinically indicated.

The recommended dosage for adults, as well as adolescents and children weighing at least 35 kg is 200 mg once daily for 6 days.

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

Special populations

Elderly (≥65 years)
No dosage adjustment is required (see section 5.2). The clinical experience in patients ≥75 years is limited.

Hepatic impairment
No dosage adjustment is required (see section 5.2).

Renal impairment
No dosage adjustment is required (see section 5.2).

Paediatric population

Tedizolid phosphate 200 mg tablets are intended for adolescents and children weighing at least 35 kg. For adolescents and children weighing less than 35 kg, tedizolid phosphate powder for concentrate for solution for infusion is available.

Method of administration

For oral use. The film-coated tablets can be taken with or without food. The time to tedizolid peak concentration with oral administration under fasting conditions is 6 hours faster than when administered with a high-fat, high-calorie meal (see section 5.2). If a rapid antibiotic effect is needed, the intravenous administration should be considered.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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 (see section 5.1).

Mitochondrial dysfunction

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

Myelosuppression

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

Peripheral neuropathy and optic nerve disorders

Peripheral neuropathy, as well as optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with another member of the oxazolidinone class with treatment durations exceeding that recommended for tedizolid phosphate. Neuropathy (optic and peripheral) has not been reported in patients treated with tedizolid phosphate at the recommended treatment duration of 6 days. All patients should be advised to report symptoms of visual impairment, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary.

Lactic acidosis

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

Hypersensitivity reactions

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

Clostridioides difficile associated diarrhoea

Clostridioides difficile associated diarrhoea (CDAD) has been reported for tedizolid phosphate (see section 4.8). CDAD may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of *C. difficile*.

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

If CDAD is suspected or confirmed, tedizolid phosphate and, if possible, other antibacterial agents not directed against *C. difficile* should be discontinued and adequate therapeutic measures should be initiated immediately. Appropriate supportive measures, antibiotic treatment of *C. difficile*, and surgical evaluation should be considered. Medicinal products inhibiting peristalsis are contraindicated in this situation.

Monoamine oxidase inhibition

Tedizolid is a reversible, non-selective inhibitor of monoamine oxidase (MAO) *in vitro* (see section 4.5).

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of oxazolidinones, including tedizolid phosphate, together with serotonergic agents (such as antidepressants and opioids) have been reported (see section 4.5).

Caution should be exercised when tedizolid is used with these medicinal products. Patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur, physicians should consider discontinuing either one or both agents.

Non-susceptible microorganisms

Prescribing tedizolid phosphate in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria.

Tedizolid is generally not active against Gram-negative bacteria.

Limitations of the clinical data

In ABSSSI, the types of infections treated were confined to cellulitis/erysipelas or major cutaneous abscesses, and wound infections only. Other types of skin infections have not been studied.

There is limited experience with tedizolid phosphate in the treatment of patients with concomitant acute bacterial skin and skin structure infections and secondary bacteraemia and no experience in the treatment of ABSSSI with severe sepsis or septic shock.

Controlled clinical studies did not include patients with neutropenia (neutrophil counts < 1 000 cells/mm^3) or severely immunocompromised patients.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

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

Pharmacodynamic interactions

Monoamine oxidase inhibition

Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) *in vitro*; however, no interaction is anticipated when comparing the IC_{50} for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies

to determine effects of 200 mg oral tedizolid phosphate at steady-state on pseudoephedrine and tyramine pressor effects were conducted in healthy volunteers. No meaningful changes in blood pressure or heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity was observed.

Potential serotonergic interactions
The potential for serotonergic interactions has not been studied in either patients or healthy volunteers (see sections 4.4 and 5.2).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of tedizolid phosphate in pregnant women. Studies in mice and rats showed developmental effects (see section 5.3). As a precautionary measure, it is preferable to avoid the use of tedizolid phosphate during pregnancy.

Breast-feeding

It is unknown whether tedizolid phosphate or its metabolites are excreted in human milk. Tedizolid is excreted in the breast milk of rats (see section 5.3). A risk to the breast-feeding infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tedizolid phosphate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of tedizolid phosphate on fertility in humans have not been studied. Animal studies with tedizolid phosphate do not indicate harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Sivextro may have a minor influence on the ability to drive and use machines as it may cause dizziness, fatigue or, uncommonly, somnolence (see section 4.8).

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) were nausea (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 phosphate alone to patients who received oral administration alone, except for a higher reported rate of gastrointestinal disorders associated with oral administration.

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 1). Increased ALT, increased AST and liver function tests abnormal were the only adverse drug reactions reported in one comparative Phase 3 study in patients 12 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 1: 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

System organ class	Frequency	Adverse reactions
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, gastro-oesophageal 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 is therefore categorised as not known.

Paediatric population
In studies of paediatric patients from birth to < 18 years of age, the safety profile of tedizolid phosphate was generally similar to the profile observed in adults.

The most common adverse reactions occurring in paediatric patients < 18 years of age receiving tedizolid phosphate in the ABSSSI clinical trials were nausea (1.1%), vomiting (1.1%), and phlebitis (1.1%).

The safety of tedizolid phosphate in adolescents 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.

The safety of tedizolid phosphate (intravenously and/or orally) was also evaluated in 2 clinical trials that included multiple dosing of 83 children < 12 years of age. These included 44 children 6 to < 12 years of age receiving a

median 9 days of dosing (range 1-12 days), 16 children 2 to < 6 years of age receiving a median 9 days of dosing (range 2-14 days), 15 children 28 days to < 2 years of age receiving a median 10 days of dosing (range 6-11 days), and 8 neonates < 28 days of age (4 full-term and 4 preterm) receiving median 3 days of dosing (range 3 days).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

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

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, other antibacterials, ATC code: J01XX11

Mechanism of action

Tedizolid phosphate is an oxazolidinone phosphate prodrug. The antibacterial activity of tedizolid is mediated by binding to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis.

Tedizolid is primarily active against Gram-positive bacteria.

Tedizolid is bacteriostatic against enterococci, staphylococci, and streptococci *in vitro*.

Resistance

The most commonly observed mutations in staphylococci and enterococci that result in oxazolidinone resistance are in one or more copies of the 23S rRNA genes (G2576U and T2500A). Organisms resistant to oxazolidinones via mutations in chromosomal genes encoding 23S rRNA or ribosomal proteins (L3 and L4) are generally cross-resistant to tedizolid.

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

The mechanism of action is different from that of non-oxazolidinone class antibacterial medicinal products; therefore, cross-resistance between tedizolid and other classes of antibacterial medicinal products is unlikely.

Antibacterial activity in combination with other antibacterial and antifungal agents

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

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for tedizolid and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Pharmacokinetic/pharmacodynamic relationship

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

In a mouse thigh infection model of *S. aureus*, the antibacterial activity of tedizolid was reduced in the absence of granulocytes. The AUC/MIC ratio to achieve bacteriostasis in neutropenic mice was at least 16 times that in immunocompetent animals (see section 4.4).

Clinical efficacy against specific pathogens

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

Acute bacterial skin and skin structure infections

- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*

- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius* and *S. constellatus*)

Antibacterial activity against other relevant pathogens

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

- *Staphylococcus lugdunensis*

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Sivextro in one or more subsets of the paediatric population in the treatment of acute bacterial skin and skin structure infections (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Oral and intravenous tedizolid phosphate is a prodrug that is rapidly converted by phosphatases to tedizolid, the microbiologically active moiety. Only the pharmacokinetic profile of tedizolid is discussed in this section.
Pharmacokinetic studies were conducted in healthy volunteers and population pharmacokinetic analyses were conducted in patients from Phase 3 studies.

Absorption

At steady-state, tedizolid mean (SD) C_{max} values of 2.2 (0.6) and 3.0 (0.7) mcg/mL and AUC values of 25.6 (8.5) and 29.2 (6.2) mcg·h/mL were similar with oral and IV administration of tedizolid phosphate, respectively. The absolute bioavailability of tedizolid is above 90%. Peak plasma tedizolid concentrations are achieved within approximately 3 hours after dosing after oral administration of tedizolid phosphate under fasted conditions.

Peak concentrations (C_{max}) of tedizolid are reduced by approximately 26% and delayed by 6 hours when tedizolid phosphate is administered after a high-fat meal relative to fasted, while total exposure ($AUC_{0-\infty}$) is unchanged between fasted and fed conditions.

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

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

Special populations

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

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

Elderly population (≥65 years)
The pharmacokinetics of tedizolid in elderly healthy volunteers (age 65 years and older, with at least 5 subjects at least 75 years old; n=14) was comparable to younger control subjects (25 to 45 years old; n=14) following administration of a single oral dose of tedizolid phosphate 200 mg.

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

The mean pharmacokinetic parameters of tedizolid after multiple dosing of tedizolid phosphate as an IV infusion and as an oral tablet for paediatric patients < 12 years of age are shown in Table 2. Compared to adult patients receiving 200 mg tedizolid phosphate once daily, steady-state tedizolid exposures (AUC_{0-24h} and C_{max}) are higher in paediatric patients < 12 years of age receiving recommended tedizolid phosphate dosing.

Table 2: Geometric Mean (%CV) predicted steady-state tedizolid population pharmacokinetic parameter estimates in paediatric patients[a] less than 12 years of age and weighing at least 35 kg

Dosage Regimen	Total Daily Dose	Route	Steady-State AUC_{0-24h} (mcg·h/mL)	Steady-State C_{max} (mcg/mL)
200 mg Once daily	200 mg	IV	38.70 (32.00)	5.02 (15.73)
		Oral (tablet)	36.96 (32.00)	3.21 (21.16)

AUC, area under the concentration-time curve; C_{max}, maximum concentration; %CV, coefficient of variation.

[a] N=16

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

Drug interaction studies

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.

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

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

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

Membrane transporters

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

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

Monoamine oxidase inhibition

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

Adrenergic agents

Two placebo-controlled crossover studies were conducted to assess the potential of 200 mg oral tedizolid phosphate at steady-state to enhance pressor responses to pseudoephedrine and tyramine in healthy individuals. No meaningful changes in blood pressure or heart rate were seen with pseudoephedrine. The median tyramine dose required to cause an increase in systolic blood pressure of $\geq$30 mmHg from pre-dose baseline was 325 mg with tedizolid phosphate 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.

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

5.3 Preclinical safety data

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

Repeated oral and intravenous dosing of tedizolid phosphate in rats in 1-month and 3-month toxicology studies produced dose- and time-dependent bone marrow hypocellularity (myeloid, erythroid, and megakaryocyte), with associated reduction in circulating RBCs, WBCs, and platelets. These effects showed evidence of reversibility and occurred at plasma tedizolid exposure levels (AUC) ≥6-fold greater than the plasma exposure associated with the human therapeutic dose. In a 1-month immunotoxicology study in rats, repeated oral dosing of tedizolid phosphate was shown to significantly reduce splenic B cells and T cells and reduce plasma IgG titres. These effects occurred at plasma tedizolid exposure levels (AUC) ≥3-fold greater than the expected human plasma exposure associated with the therapeutic dose.

In studies in juvenile rats, no specific, nor unique target organs of toxicity were observed compared to those already identified in the repeat oral dose toxicity studies in adult rats. However, the exposure at the no observed adverse effect level (NOAEL) (based on $AUC_{0\text{-}24h}$) of the juvenile toxicity study was 2-fold lower compared to the exposure in the 28-day study in adult rats. Accordingly, plasma exposure levels in the juvenile toxicity study were similar to those in paediatric patients at the human therapeutic dose.

A special neuropathology study was conducted in pigmented Long Evans rats administered tedizolid phosphate daily for up to 9 months. This study used sensitive morphologic evaluation of perfusion-fixed peripheral and central nervous system tissue. No evidence of neurotoxicity, including neurobehavioral changes or optic or peripheral neuropathy, was associated with tedizolid after 1, 3, 6 or 9 months of oral administration up to doses with plasma exposure levels (AUC) up to 8-fold greater than the expected human plasma exposure at the oral therapeutic dose.

Tedizolid phosphate was negative for genotoxicity in all *in vitro* assays (bacterial reverse mutation [Ames], Chinese hamster lung [CHL] cell chromosomal aberration) and in all *in vivo* tests (mouse bone marrow micronucleus, rat liver unscheduled DNA synthesis). Tedizolid, generated from tedizolid phosphate after metabolic activation (*in vitro* and *in vivo*), was also

tested for genotoxicity. Tedizolid was positive in an *in vitro* CHL cell chromosomal aberration assay, but negative for genotoxicity in other *in vitro* assays (Ames, mouse lymphoma mutagenicity) and *in vivo* in a mouse bone marrow micronucleus assay.

Tedizolid phosphate had no adverse effects on the fertility or reproductive performance of male rats, including spermatogenesis, at oral doses up to the maximum tested dose of 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 $\geq$ 5.3-fold for males and $\geq$ 4.2-fold for females relative to tedizolid plasma $AUC_{0\text{-}24h}$ levels at the human oral therapeutic dose.

Embryo-foetal development studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4-fold and 6-fold, respectively, those expected in humans. In embryo-foetal studies, tedizolid phosphate was shown to produce foetal developmental toxicities in mice and rats. Foetal developmental effects occurring in mice in the absence of maternal toxicity included reduced foetal weights and an increased incidence of costal cartilage fusion (an exacerbation of the normal genetic predisposition to sternal variations in the CD-1 strain of mice) at the high dose of 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 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.

Tedizolid is excreted into the milk of lactating rats and the concentrations observed were similar to those in maternal plasma.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Mannitol
Povidone
Crospovidone
Magnesium stearate

Film coat

Polyvinyl alcohol
Titanium dioxide (E171)
Macrogol
Talc
Yellow iron oxide (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

6 × 1 tablets in aluminium/Polyethylene Terephthalate (PET)/Paper foil and polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) clear film perforated child-resistant unit-dose blisters.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme (UK) Limited
120 Moorgate
London
EC2M 6UR
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 53095/0062

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

01/05/2025