This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

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 is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (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 film-coated tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral presentation when clinically indicated.

*Recommended dose and duration*

The recommended dosage is 200 mg once daily for 6 days.

The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established (see section 4.4).

*Missed dose*

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.
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
The safety and efficacy of tedizolid phosphate in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

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 <1000 cells/mm³) have not been investigated. In an animal model of infection, the antibacterial activity of tedizolid phosphate 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 Sivextro.

Myelosuppression

Decreased platelets, decreased haemoglobin and decreased neutrophils have been observed in a few subjects during treatment with tedizolid phosphate. In cases where tedizolid was discontinued, the affected haematological parameters have returned back to pre-treatment levels. Myelosuppression (including anaemia, leucopenia, 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.

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 Sivextro. 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.

Clostridium difficile associated diarrhoea

*Clostridium 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 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 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.

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 phosphate is generally not active against Gram-negative bacteria.
Women of childbearing potential

Women of childbearing potential must use reliable contraception while taking tedizolid phosphate. It is currently unknown whether tedizolid phosphate may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives must use an additional method of contraception (see section 4.5).

Limitations of the clinical data

The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established.

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

There is limited experience with tedizolid phosphate in the treatment of patients with concomitant acute bacterial skin and skin structure infections and secondary bacteremia 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 <1000 cells/mm³) or severely immunocompromised patients.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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, triazolam, alfentanil, cyclosporine, fentanyl, pimozide, 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 (see section 4.4). This is not a complete list; please consult the SmPC of the co-administered medicinal product.

There is a potential for interaction between oral tedizolid phosphate and orally administered substrates of Breast Cancer Resistance Protein (BCRP). The BCRP inhibition could result in increased exposure of medicinal products such as imatinib, lapatinib, methotrexate, pitavastatin, rosvastatin, sulfasalazine, and topotecan (see section 5.2). If possible, an intermission of the co-administered medicinal product should be considered during the six days of treatment with tedizolid phosphate.

Pharmacodynamic interactions

Monoamine oxidase inhibition

Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) in vitro; however, no interaction is anticipated when comparing the IC₅₀ for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies to determine effects of 200 mg oral Sivextro at steady state on pseudoephedrine and tyramine pressor effects were conducted in healthy volunteers. No meaningful changes in blood pressure, heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity were observed.

Potential serotonergic interactions

The potential for serotonergic interactions has not been studied in either patients or healthy volunteers (see section 5.2).
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 Sivextro 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

No studies on the effects on the ability to drive and use machines have been performed. 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

The safety of tedizolid phosphate has been evaluated in a total of 1,485 subjects receiving at least one dose of tedizolid phosphate administered either orally or intravenously. The primary safety data base is the Phase 3 clinical studies in which 662 subjects received 200 mg tedizolid phosphate orally and or intravenously (331/662 patients) for a maximum of 6 days.

Approximately 22.4% of patients treated with Sivextro in Phase 3 clinical studies (n=662) experienced at least one treatment-emergent adverse reaction. The most frequently reported adverse reactions occurring in patients receiving tedizolid phosphate in the pooled controlled Phase 3 clinical studies (tedizolid 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.

Tabulated list of adverse reactions

The following adverse reactions have been identified in two comparative pivotal Phase 3 studies with Sivextro (Table 1). 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. 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).
Table 1: Frequency of adverse reactions by System Organ Class in pooled Phase 3 comparative clinical studies

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Vulvovaginal mycotic infection</td>
<td>Fungal infection</td>
</tr>
<tr>
<td></td>
<td>Vulvovaginal candidiasis</td>
<td>Abscess</td>
</tr>
<tr>
<td></td>
<td>Clostridium difficile colitis</td>
<td>Dermatophytosis</td>
</tr>
<tr>
<td></td>
<td>Oral candidiasis</td>
<td>Respiratory tract infection</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Lymphadenopathy</td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Drug hypersensitivity</td>
<td></td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Dehydration</td>
<td>Diabetes mellitus inadequate control</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep disorder</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nightmare</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Somnolence</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Dysgeusia</td>
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<tr>
<td></td>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Paraesthesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoaesthesia</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vitreous floaters</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Bradycardia</td>
<td></td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hot flush</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>Nasal dryness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pulmonary congestion</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Abdominal discomfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry mouth</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dyspepsia</td>
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<tr>
<td></td>
<td></td>
<td>Abdominal pain upper</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Flatulence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrooesophageal reflux disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haematochezia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Retching</td>
</tr>
<tr>
<td>Skin And subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>Hyperhidrosis</td>
</tr>
<tr>
<td></td>
<td>Generalised</td>
<td>Pruritus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urticaria</td>
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<tr>
<td></td>
<td></td>
<td>Alopecia</td>
</tr>
</tbody>
</table>
Reported adverse reactions

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash erythematous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash generalised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acne</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus allergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td></td>
<td></td>
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<tr>
<td>Rash papular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash pruritic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle spasms</td>
<td></td>
<td></td>
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<tr>
<td>Back pain</td>
<td></td>
<td></td>
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<tr>
<td>Limb discomfort</td>
<td></td>
<td></td>
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<tr>
<td>Neck pain</td>
<td></td>
<td></td>
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<tr>
<td>Urine odor abnormal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vulvovaginal pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grip strength decreased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transaminases increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell count decreased</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**4.9 Overdose**

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

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: not yet assigned. ATC code: not yet assigned

**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

Minimum inhibitory concentration (MIC) breakpoints determined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Minimum Inhibitory Concentrations (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Susceptible (≤S)</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td>0.5</td>
</tr>
<tr>
<td>Beta haemolytic streptococci of Groups A,B,C,G</td>
<td>0.5</td>
</tr>
<tr>
<td>Viridans group streptococci (<em>Streptococcus anginosus</em> group only)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

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*. 

9
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) $C_{\text{max}}$ 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 Sivextro under fasted conditions.

Peak concentrations ($C_{\text{max}}$) 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 sulfate conjugate. Following single oral administration of 14C-labeled 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 6-7 L/h.

**Linearity/non-linearity**

Tedizolid demonstrated linear pharmacokinetics with regard to dose and time. The C\textsubscript{max} and AUC of tedizolid increased approximately dose proportionally within the single oral dose range of 200 mg to 1200 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 Sivextro to 8 subjects with severe renal impairment defined as eGFR <30 mL/min, the C\textsubscript{max} was basically unchanged and AUC\textsubscript{0-\infty} was changed by less than 10% compared to 8 matched healthy subject controls. Hemodialysis 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 Sivextro, 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 Sivextro 200 mg.

**Paediatric population**

The pharmacokinetics of tedizolid were evaluated in adolescent subjects (12 to 17 years; n=20) following administration of a single oral or IV dose of Sivextro 200 mg. The mean C\textsubscript{max} and AUC\textsubscript{0-\infty} for oral or IV administration of tedizolid 200 mg were similar in adolescent and in healthy adult subjects.

**Gender**

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

**Drug interaction studies**

**Drug metabolizing enzymes**

*In vitro* studies in human liver microsomes indicate that tedizolid phosphate and tedizolid do not significantly inhibit metabolism mediated by any of the following cytochrome P450 isoenzymes (CYP1A2, CYP2C19, CYP2A6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4). Induction of CYP3A4 mRNA was observed *in vitro* in hepatocytes (see section 4.5). Multiple sulfotransferases (SULT) isoforms were identified *in vitro* that are capable of conjugating tedizolid (spanning multiple families; SULT1A1, SULT1A2, and SULT2A1), which suggests that no
single isozyme is critical to the clearance of tedizolid.

Membrane transporters
The potential for tedizolid or tedizolid phosphate to inhibit transport of probe substrates of important drug uptake (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2) and efflux transporters (P-gp and BCRP) was tested in vitro. No consistent inhibition of any transporter was observed with the exception of BCRP, which was inhibited by tedizolid. Tedizolid inhibited OATP1B1 by ~30% at 30 µM.

Monoamine oxidase inhibition
Tedizolid is a reversible inhibitor of MAO in vitro; however, no interaction is anticipated when comparing the IC50 and the anticipated plasma exposures in man. No evidence of MAO-A inhibition was observed in Phase 1 studies specifically designed to investigate the potential for this interaction.

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

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

A special neuropathology study was conducted in pigmented Long Evans rats administered tedizolid phosphate daily for up to 9 months. This study used sensitive morphologic evaluation of perfusion-fixed peripheral and central nervous system tissue. No evidence of neurotoxicity, including neurobehavioral changes or optic or peripheral neuropathy, was associated with tedizolid after 1, 3, 6 or 9 months of oral administration up to doses with plasma 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 ≥5.3-fold for males and ≥4.2-fold for females relative to tedizolid plasma AUC₀₋₂₄ levels at the human oral therapeutic dose.

Embryofetal 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 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 sternabae, 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.

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 tablet in aluminum foil and polyvinyl chloride (PVC)/polyvinylidene chloride (PVdC) clear film perforated unit-dose blisters.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Cubist (UK) Ltd
Unit 1 Horizon Business Village
No 1, Brooklands Road
Weybridge
Surrey KT13 0RU
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/991/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. **NAME OF THE MEDICINAL PRODUCT**

Sivextro 200 mg powder for concentrate for solution for infusion

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial contains disodium tedizolid phosphate corresponding to 200 mg tedizolid phosphate.

After reconstitution each mL contains 50 mg tedizolid phosphate.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Powder for concentrate for solution for infusion (powder for concentrate).

White to off-white powder.

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Sivextro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults (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 film-coated tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral one when clinically indicated.

**Recommended dose and duration**

The recommended dosage is 200 mg once daily for 6 days.

The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established in patients (see section 4.4).

**Missed dose**

If a dose is missed it should be given to the patient as soon as possible anytime up to 8 hours prior to the next scheduled dose. If less than 8 hours remains before the next dose, then the physician should wait until the next scheduled dose. A double dose should not be given to compensate for a missed dose.
**Elderly (≥65 years)**
No dosage adjustment is required (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**
The safety and efficacy of tedizolid phosphate in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology can be made.

**Method of administration**
Sivextro must be administered by intravenous infusion over a 60-minute period.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6

**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 <1000 cells/mm³) have not been investigated. In an animal model of infection, the antibacterial activity of tedizolid phosphate 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 Sivextro

**Myelosuppression**
Decreased platelets, decreased haemoglobin and decreased neutrophils have been observed in a few subjects during treatment with tedizolid phosphate. In cases where tedizolid was discontinued, the affected haematological parameters have returned back to pre-treatment levels. Myelosuppression (including anaemia, leucopenia, 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.

**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 Sivextro. 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.

**Clostridium difficile associated diarrhoea**

*Clostridium 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. Medinical 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 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 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.

**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 phosphate is generally not active against Gram-negative bacteria.
Women of childbearing potential

Women of childbearing potential must use reliable contraception while taking tedizolid phosphate. It is currently unknown whether tedizolid phosphate may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives must use an additional method of contraception (see section 4.5).

Limitations of the clinical data

The safety and efficacy of tedizolid phosphate when administered for periods longer than 6 days have not been established.

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

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

Controlled clinical studies did not include patients with neutropenia (neutrophil counts <1000 cells/mm³) or severely immunocompromised patients.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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, triazolam, alfentanil, cyclosporine, fentanyl, pimozide, 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 (see section 4.4). This is not a complete list; please consult the SmPC of the co-administered medicinal product.

There is a potential for tedizolid phosphate to inhibit organic anion transporter (OATP1B1) based on in vitro data. 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. If possible, an intermission of the co-administered medicinal product should be considered during the six days of treatment with tedizolid phosphate.

Pharmacodynamic interactions

Monoamine oxidase inhibitors

Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) in vitro; however, no interaction is anticipated when comparing the IC₅₀ for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies to determine effects of 200 mg oral Sivextro at steady state on pseudoephedrine and tyramine pressor effects were conducted in healthy volunteers. No meaningful changes in blood pressure, heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity were observed.

Potential serotonergic interactions

The potential for serotonergic interactions has not been studied in either patients or healthy volunteers (see section 5.2).
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 Sivextro 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

No studies on the effects on the ability to drive and use machines have been performed. 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

The safety of tedizolid phosphate has been evaluated in a total of 1485 subjects receiving at least one dose of tedizolid phosphate administered either orally or intravenously. The primary safety database is the Phase 3 clinical studies in which 662 subjects received 200 mg tedizolid phosphate orally and/or intravenously (331/662 patients) for a maximum of 6 days.

Approximately 22.4% of patients treated with Sivextro in Phase 3 clinical studies (n=662) experienced at least one treatment-emergent adverse reaction. The most frequently reported adverse reactions occurring in patients receiving tedizolid phosphate in the pooled controlled Phase 3 clinical studies (tedizolid 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.

Tabulated list of adverse reactions

The following adverse reactions have been identified in two comparative pivotal Phase 3 studies with Sivextro (Table 1). 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. 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).
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Vulvovaginal mycotic infection</td>
<td>Fungal infection</td>
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<td></td>
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<td>Vulvovaginal candidiasis</td>
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<td></td>
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<td>Abscess</td>
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<td></td>
<td></td>
<td>Clostridium difficile colitis</td>
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<td></td>
<td></td>
<td>Dermatophytosis</td>
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<tr>
<td></td>
<td></td>
<td>Oral candidiasis</td>
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<td></td>
<td></td>
<td>Respiratory tract infection</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>Lymphadenopathy</td>
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<tr>
<td>Immune system disorders</td>
<td>Drug hypersensitivity</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Dehydration</td>
<td>Diabetes mellitus inadequate control</td>
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<td></td>
<td></td>
<td>Hyperkalaemia</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
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<td></td>
<td>Sleep disorder</td>
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<td></td>
<td>Anxiety</td>
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<tr>
<td></td>
<td>Nightmare</td>
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<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>Somnolence</td>
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<td></td>
<td>Dizziness</td>
<td>Dysgeusia</td>
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<td></td>
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<td>Tremor</td>
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<td>Paraesthesia</td>
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<td>Hypoesthesia</td>
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<tr>
<td>Eye disorders</td>
<td>Vision blurred</td>
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<td></td>
<td>Vitreous floaters</td>
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<tr>
<td>Cardiac disorders</td>
<td>Bradycardia</td>
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<tr>
<td>Vascular disorders</td>
<td>Flushing</td>
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<tr>
<td></td>
<td>Hot flush</td>
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<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td></td>
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<tr>
<td></td>
<td>Nasal dryness</td>
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<td></td>
<td>Pulmonary congestion</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea</td>
<td>Abdominal pain</td>
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<tr>
<td></td>
<td>Diarrhoea</td>
<td>Constipation</td>
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<td></td>
<td>Vomiting</td>
<td>Abdominal discomfort</td>
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<td></td>
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<td>Dry mouth</td>
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<td></td>
<td>Dyspepsia</td>
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<td></td>
<td>Abdominal pain upper</td>
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<td></td>
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<td>Flatulence</td>
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<td>Gastrooesophageal reflux disease</td>
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<td></td>
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<td>Haematochezia</td>
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<td></td>
<td></td>
<td>Retching</td>
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<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus Generalised</td>
<td>Hyperhidrosis</td>
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<td></td>
<td></td>
<td>Pruritus</td>
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<td></td>
<td></td>
<td>Rash</td>
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<td></td>
<td></td>
<td>Urticaria</td>
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<td></td>
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<td>Alopecia</td>
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<tr>
<td>System Organ Class</td>
<td>Common</td>
<td>Uncommon</td>
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<tr>
<td></td>
<td>Rash erythematous</td>
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<td></td>
<td>Rash generalised</td>
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<tr>
<td></td>
<td>Acne</td>
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<td></td>
<td>Pruritus allergic</td>
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<td></td>
<td>Rash maculo-papular</td>
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<td></td>
<td>Rash papular</td>
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<td></td>
<td>Rash pruritic</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
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<td></td>
<td>Muscle spasms</td>
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<td></td>
<td>Back pain</td>
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<td>Limb discomfort</td>
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<td>Neck pain</td>
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<td>Renal and urinary disorders</td>
<td>Urine odor abnormal</td>
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<td>Reproductive and breast disorders</td>
<td>Vulvovaginal pruritus</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
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<td></td>
<td>Chills</td>
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<td></td>
<td>Infusion site pain</td>
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<td></td>
<td>Infusion site phlebitis</td>
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<td></td>
<td>Irritability</td>
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<td></td>
<td>Pyrexia</td>
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<td></td>
<td>Infusion related reaction</td>
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<tr>
<td></td>
<td>Peripheral oedema</td>
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<tr>
<td>Investigations</td>
<td>Grip strength decreased</td>
<td></td>
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<td></td>
<td>Transaminases increased</td>
<td></td>
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<tr>
<td></td>
<td>White blood cell count decreased</td>
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</tbody>
</table>

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 national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: not yet assigned. ATC code: not yet assigned

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

Minimum inhibitory concentration (MIC) breakpoints determined by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) are:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Minimum Inhibitory Concentrations (mg/L)</th>
<th>Susceptible (≤S)</th>
<th>Resistant (R&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus</em> spp.</td>
<td></td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Beta haemolytic <em>Streptococci</em> of Groups A,B,C,G</td>
<td></td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Viridans group streptococci (<em>Streptococcus anginosus</em> group only)</td>
<td></td>
<td>0.25</td>
<td>0.25</td>
</tr>
</tbody>
</table>

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) $C_{\text{max}}$ 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 Sivextro under fasted conditions.

Peak concentrations ($C_{\text{max}}$) 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 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 sulphotransferase (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 sulfate conjugate. Following single oral administration of 14C-labeled 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 6-7 L/h.

Linearity/non-linearity

Tedizolid demonstrated linear pharmacokinetics with regard to dose and time. The Cmax and AUC of tedizolid increased approximately dose proportionally within the single oral dose range of 200 mg to 1200 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 Sivextro to 8 subjects with severe renal impairment defined as eGFR <30 mL/min, the Cmax was basically unchanged and AUC0-∞ was changed by less than 10% compared to 8 matched healthy subject controls. Hemodialysis 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 Sivextro, 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 Sivextro 200 mg.

Paediatric population

The pharmacokinetics of tedizolid were evaluated in adolescent subjects (12 to 17 years; n=20) following administration of a single oral or IV dose of Sivextro 200 mg. The mean Cmax and AUC0-∞ for oral or IV administration of tedizolid 200 mg were similar in adolescent and in healthy adult subjects.

Gender

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

Drug interaction studies

Drug metabolizing enzymes

In vitro studies in human liver microsomes indicate that tedizolid phosphate and tedizolid do not significantly inhibit metabolism mediated by any of the following cytochrome P450 isoenzymes (CYP1A2, CYP2C19, CYP2A6, CYP2C8, CYP2C9, CYP2D6, and CYP3A4). Induction of CYP3A4 mRNA was observed in vitro in hepatocytes (see section 4.5). Multiple sulfotransferases (SULT) isoforms were identified in vitro that are capable of conjugating tedizolid (spanning multiple families; SULT1A1, SULT1A2, and SULT2A1), which suggests that no
single isozyme is critical to the clearance of tedizolid.

Membrane transporters
The potential for tedizolid or tedizolid phosphate to inhibit transport of probe substrates of important drug uptake (OAT1, OAT3, OATP1B1, OATP1B3, OCT1, and OCT2) and efflux transporters (P-gp and BCRP) was tested in vitro. No consistent inhibition of any transporter was observed with the exception of BCRP, which was inhibited by tedizolid. Tedizolid inhibited OATP1B1 by ~30% at 30 µM.

Monoamine oxidase inhibition
Tedizolid is a reversible inhibitor of MAO in vitro; however, no interaction is anticipated when comparing the IC50 and the anticipated plasma exposures in man. No evidence of MAO-A inhibition was observed in Phase 1 studies specifically designed to investigate the potential for this interaction.

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

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

A special neuropathology study was conducted in pigmented Long Evans rats administered tedizolid phosphate daily for up to 9 months. This study used sensitive morphologic evaluation of perfusion-fixed peripheral and central nervous system tissue. No evidence of neurotoxicity, including neurobehavioral changes or optic or peripheral neuropathy, was associated with tedizolid after 1, 3, 6 or 9 months of oral administration up to doses with plasma 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 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 AUC₀₋₂₄ levels at the human oral therapeutic dose.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6. Sivextro is incompatible with any solutions containing divalent cations (e.g., Ca²⁺, Mg²⁺), including Lactated Ringer’s Injection and Hartmann's Solution.

6.3 Shelf life

3 years.

After reconstitution, it should be used within 4 hours at room temperature or 24 hours when stored at 2°C to 8°C.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.
6.5 **Nature and contents of container**

Type I (10 ml) clear borosilicate tubing glass vial with a siliconised grey chlorobutyl rubber stopper. 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 vials are intended for single use only.

It must be administered as an intravenous infusion only. It must not be administered as an intravenous bolus.

Aseptic technique must be followed in preparing the infusion solution. The contents of Sivextro should be reconstituted with 4 ml of water for injections, and be swirled gently until the powder has dissolved entirely. Shaking or rapid movement should be avoided as it may cause foaming.

For administration, the reconstituted solution must be further diluted in 250 ml of sodium chloride 0.9% solution for injection. The bag should not be shaken. The resulting solution is a clear colourless or light-yellow solution and should be administered over approximately 1 hour.

Only limited data are available on the compatibility of Sivextro with other intravenous substances, therefore additives or other medicinal products should not be added to Sivextro single use vials or infused simultaneously. If the same intravenous line is used for sequential infusion of several different medicinal products, the line should be flushed before and after infusion with 0.9% sodium chloride.

The reconstituted solution should be inspected visually for particulate matter prior to administration. Reconstituted solutions containing visible particles should be discarded.

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

7. **MARKETING AUTHORISATION HOLDER**

Cubist (UK) Ltd
Unit 1 Horizon Business Village
No 1, Brooklands Road
Weybridge
Surrey KT13 0RU
United Kingdom

8. **MARKETING AUTHORISATION NUMBER(S)**

EU/1/15/991/002
EU/1/15/991/003

9. **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION**

10. **DATE OF REVISION OF THE TEXT**

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

PATHEON ITALIA S.P.A.
2° Trav. SX Via Morolense, 5, Ferentino, 03013, Italy

PATHEON UK LIMITED
Kingfisher Drive, Covingham, Swindon, SN3 5BZ, United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT
Sivextro 200 mg film-coated tablets
tedizolid phosphate

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each film-coated tablet contains 200 mg tedizolid phosphate.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS
6 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE
11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cubist (UK) Ltd
Surrey KT13 0RU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/991/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sivextro
**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTERS**

1. **NAME OF THE MEDICINAL PRODUCT**

   Sivextro 200 mg tablets
tedizolid phosphate

2. **NAME OF THE MARKETING AUTHORISATION HOLDER**

   Cubist (UK) Ltd

3. **EXPIRY DATE**

   EXP

4. **BATCH NUMBER**

   Lot

5. **OTHER**

   Peel, then push
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

**OUTER CARTON (VIAL)**

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<tbody>
<tr>
<td>Sivextro 200 mg powder for concentrate for solution for infusion tedizolid phosphate</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each vial contains disodium tedizolid phosphate corresponding to 200 mg tedizolid phosphate. After reconstitution each ml contains 50 mg tedizolid phosphate.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>mannitol, sodium hydroxide, hydrochloric acid</td>
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</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Powder for concentrate for solution for infusion</td>
</tr>
<tr>
<td>1 vial</td>
</tr>
<tr>
<td>6 vials</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
<tr>
<td><strong>Intravenous use after reconstitution and dilution</strong></td>
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<tr>
<td>For single use only</td>
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<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the sight and reach of children.</td>
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<table>
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<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
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<table>
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<tr>
<th>8. EXPIRY DATE</th>
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<tr>
<td>EXP</td>
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<tr>
<th>9. SPECIAL STORAGE CONDITIONS</th>
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</tbody>
</table>


10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Cubist (UK) Ltd
Surrey KT13 0RU
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/991/002 1 vial
EU/1/15/991/003 6 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sivextro
<table>
<thead>
<tr>
<th>MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS</th>
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<td>VIAL LABEL</td>
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<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</th>
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</thead>
<tbody>
<tr>
<td>Sivextro 200 mg powder for concentrate</td>
</tr>
<tr>
<td>tedizolid phosphate</td>
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<tr>
<td>IV</td>
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</table>

<table>
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<tr>
<th>2. METHOD OF ADMINISTRATION</th>
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</thead>
<tbody>
<tr>
<td>Read the package leaflet before use.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>3. EXPIRY DATE</th>
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<tbody>
<tr>
<td>EXP</td>
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</table>

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<tr>
<th>4. BATCH NUMBER</th>
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</thead>
<tbody>
<tr>
<td>Lot</td>
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<table>
<thead>
<tr>
<th>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 mg</td>
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</table>

<table>
<thead>
<tr>
<th>6. OTHER</th>
</tr>
</thead>
</table>
B. PACKAGE LEAFLET
This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet
1. What Sivextro is and what it is used for
2. What you need to know before you take Sivextro
3. How to take Sivextro
4. Possible side effects
5. How to store Sivextro
6. Contents of the pack and other information

1. What Sivextro is and what it is used for

Sivextro is an antibiotic that contains the active substance tedizolid phosphate. It belongs to a group of medicines called "oxazolidinones."

It is used to treat adults with infections of the skin and tissues below the skin.

It works by stopping the growth of certain bacteria which can cause serious infections.

2. What you need to know before you take Sivextro

Do not take Sivextro if you are allergic to tedizolid phosphate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Your doctor will have decided if Sivextro is suitable to treat your infection.

Talk to your doctor or nurse before taking Sivextro if any of the following apply to you:
- are suffering from diarrhoea, or have suffered from diarrhoea whilst (or up to 2 months after) taking antibiotics in the past.
- are allergic to other medicines belonging to the group “oxazolidinones” (e.g., linezolid, cycloserine).
- are taking certain medicines known as tricyclics or SSRIs (selective serotonin reuptake inhibitors) to treat depression, for example,
  - amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, and sertraline.
- are taking certain medicines used to treat migraine known as “triptans,” such as sumatriptan and
zolmitriptan.
- are taking certain medicines known as MAOIs to treat depression, for example,
- phenelzine, isocarboxazid, selegiline, and moclobemide.

Ask your doctor or pharmacist if you are not sure whether you are taking any of these medicines.

**Diarrhoea**
Contact your doctor straight away if you suffer from diarrhoea during or after your treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor.

**Resistance to antibiotics**
Bacteria can become resistant to treatment with antibiotics over time. This is when antibiotics cannot stop the growth of bacteria and treat your infection. Your doctor will decide if you should be given Sivextro to treat your infection.

Certain side effects have been observed with another member of the oxazolidinone class when administered over a duration exceeding that recommended for Sivextro. Tell your doctor straight away if you suffer from any of the following while taking Sivextro:
- a low white blood cell count
- anaemia (low red blood cells)
- bleeding or bruising easily
- loss of sensitivity in your hands or feet (such as numbness, prickling/tingling, or sharp pains)
- any problems with your eyesight such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.

**Children and adolescents**
This medicine should not be used in children and adolescents as it has not been studied enough in these populations.

**Other medicines and Sivextro**
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. It is especially important that you tell your doctor if you are also taking:
- midazolam or triazolam (used to treat anxiety or as muscle relaxants)
- alfentanil or fentanyl (used to treat severe pain)
- pimozide (used to treat Tourette’s syndrome and mental illness)
- quinidine (used to treat abnormal heart rhythms)
- cyclosporine, sirolimus, tacrolimus (used before or after transplant surgery)
- warfarin (used as a blood thinner or to treat blood clots)
- efavirenz (used to treat HIV infection)
- digoxin (used to treat heart failure)
- imatinib, lapatinib (used to treat cancer)
- methotrexate (used to treat cancer or rheumatoid arthritis)
- sulfasalazine (used to treat inflammatory bowel diseases)
- topotecan (used to treat cancer)
- statins such as atorvastatin, fluvastatin, pitavastatin, lovastatin (used to lower blood cholesterol)
- repaglinide, glyburide (used to treat high blood sugar)
- bosentan (used to treat high blood pressure in the lungs)
- valsartan, olmesartan (used to treat high blood pressure)

Sivextro can interfere with the effects of these medicines. Your doctor will explain more.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is not known if Sivextro passes into breast milk in humans. Ask your doctor for advice before
breast-feeding your baby.

If you are a woman who could become pregnant you must use reliable contraception while you are taking Sivextro. Contraceptives that release hormones (e.g., birth control pills, skin patches, implants, and certain intrauterine devices [IUDs]) may not work effectively when taken together with this medicine. Women using these types of hormonal contraceptives must also use a second ‘barrier’ method (such as condoms or diaphragm with spermicide). Contact your doctor straight away if you become pregnant while you are taking Sivextro.

**Driving and using machines**
Do not drive or use machines if you feel dizzy or tired after taking this medicine.

### 3. How to take Sivextro

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose is one 200 mg tablet once a day for 6 days. The tablets are swallowed whole and can be taken with or without food or drink.

Talk to a doctor if you do not feel better, or if you feel worse after 6 days.

**If you take more Sivextro than you should**
Contact your doctor, pharmacist or nearest hospital casualty department as soon as possible if you have taken more tablets than you should, and take your medicine with you.

**If you forget to take Sivextro**
If you forget to take your medicine, take the dose 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 wait until the next scheduled dose. Do not take a double dose to make up for a forgotten dose. If in any doubt, contact your pharmacist for advice.

You should take all 6 tablets to complete your course of treatment, even if you have missed a dose.

**If you stop taking Sivextro**
If you stop taking Sivextro without the advice of your doctor, your symptoms may get worse. Talk to your doctor or pharmacist before you stop taking your medicine.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Contact your doctor straight away** if you suffer from diarrhoea during or after your treatment.

**Other side effects may include:**
Common side effects (may affect up to 1 in 10 people)

- Nausea
- Vomiting
- Headache
- Itching all over the body
- Tiredness
- Dizziness

Uncommon side effects (may affect up to 1 in 100 people)
• Fungal infections of skin, mouth and vagina (oral / vaginal thrush)
• Itching (including itching due to allergic reaction), hair loss, acne, red and/or itchy rash or hives, excessive sweating
• Decrease or loss of skin sensitivity, tingling/prickling skin sensation
• Hot flush or blushing/redness in the face, neck or upper chest
• Abscess (swollen, pus-filled lump)
• Vaginal infection, inflammation or itching
• Anxiety, irritability, Shaking or trembling
• Respiratory tract (sinuses, throat and chest) infection
• Dryness in the nose, congestion in the chest, cough
• Sleepiness, abnormal sleep pattern, difficulty sleeping, nightmares (unpleasant/disturbing dreams)
• Dry mouth, constipation, indigestion, pain/discomfort in the belly (abdomen), retching, dry heaving, bright red blood in the stool
• Acid reflux disease (heartburn, pain or difficulty swallowing), flatulence/passing wind,
• Joint pain, muscle spasms, back pain, neck pain, pain/discomfort in limbs, decrease of grip strength
• Blurred vision, ‘floaters’ (small shapes seen floating in the field of vision)
• Swollen or enlarged lymph nodes
• Allergic reaction
• Dehydration
• Poor control of diabetes
• Abnormal sense of taste
• Slow heartbeat
• Fever
• Swelling in ankles and/or feet
• Abnormal smelling urine, abnormal blood tests

**Reporting of side effects**
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. **How to store Sivextro**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton or blister label after “EXP”. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. **Contents of the pack and other information**

**What Sivextro contains**
• The active substance is tedizolid phosphate. Each film-coated tablet contains 200 mg of tedizolid phosphate.
• The other ingredients are microcrystalline cellulose, mannitol, povidone, crospovidone and magnesium stearate within the tablet core. The film coat of the tablet contains polyvinyl alcohol, titanium dioxide (E171), macrogol, talc and yellow iron oxide (E172).
What Sivextro looks like and contents of the pack
Sivextro is an oval, yellow film-coated tablet imprinted with ‘TZD’ on one side and ‘200’ on the other side.

It is available in 6 × 1 tablets in perforated unit-dose blisters.

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No 1, Brooklands Road
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United Kingdom

Manufacturer
Patheon UK Limited
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Covingham
Swindon
Wiltshire SN3 5BZ
United Kingdom

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.
Package leaflet: Information for the patient

Sivextro 200 mg powder for concentrate for solution for infusion
tedizolid phosphate

This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start receiving this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sivextro is and what it is used for
2. What you need to know before you are given Sivextro
3. How you will be given Sivextro
4. Possible side effects
5. How to store Sivextro
6. Contents of the pack and other information

1. What Sivextro is and what it is used for

Sivextro is an antibiotic that contains the active substance tedizolid phosphate. It belongs to a group of medicines called “oxazolidinones.”

It is used to treat adults with infections of the skin and tissues below the skin in adults.

It works by stopping the growth of certain bacteria which can cause serious infections.

2. What you need to know before you are given Sivextro

Do not use Sivextro:
- if you are allergic to tedizolid phosphate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Your doctor will have decided if Sivextro is suitable to treat your infection.

Talk to your doctor or nurse before being given Sivextro if any of the following apply to you:
- are suffering from diarrhoea, or have suffered from diarrhoea whilst (or up to 2 months after) taking antibiotics in the past.
- are allergic to other medicines belonging to the group “oxazolidinones” (e.g., linezolid, cycloserine).
- are taking certain medicines known as tricycles or SSRIs (selective serotonin reuptake inhibitors) to treat depression, for example,
  - amitriptyline, cipramil, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, lofepramine, paroxetine, and sertraline.
- are taking certain medicines used to treat migraine known as “triptans,” such as sumatriptan and
are taking certain medicines known as MAOIs to treat depression, for example, phenelzine, isocarboxazid, selegiline, and moclobemide.

Ask your doctor or pharmacist if you are not sure whether you are taking any of these medicines.

**Diarrhoea**
Contact your doctor straight away if you suffer from diarrhoea during or after your treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor.

**Resistance to antibiotics**
Bacteria can become resistant to treatment with antibiotics over time. This is when antibiotics cannot stop the growth of bacteria and treat your infection. Your doctor will decide if you should be given Sivextro to treat your infection.

Certain side effects have been observed with another member of the oxazolidinone class when administered over a duration exceeding that recommended for Sivextro. Tell your doctor straight away if you suffer from any of the following while taking Sivextro:
- a low white blood cell count
- anaemia (low red blood cells)
- bleeding or bruising easily
- loss of sensitivity in your hands or feet (such as numbness, prickling/tingling, or sharp pains)
- any problems with your eyesight such as blurred vision, changes in colour vision, difficulty in seeing detail or if your field of vision becomes restricted.

**Children and adolescents**
This medicine should not be used in children and adolescents as it has not been studied enough in these populations.

**Other medicines and Sivextro**
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. It is especially important that you tell your doctor if you are also taking:
- midazolam or triazolam (used to treat anxiety or as muscle relaxants)
- alfentanil or fentanyl (used to treat severe pain)
- pimozide (used to treat Tourette’s syndrome and mental illness)
- quinidine (used to treat abnormal heart rhythms)
- cyclosporine, sirolimus, tacrolimus (used before or after transplant surgery)
- warfarin (used as a blood thinner or to treat blood clots)
- efavirenz (used to treat HIV infection)
- digoxin (used to treat heart failure)
- imatinib, lapatinib (used to treat cancer)
- methotrexate (used to treat cancer or rheumatoid arthritis)
- sulfasalazine (used to treat inflammatory bowel diseases)
- topotecan (used to treat cancer)
- statins such as atorvastatin, fluvastatin, pitavastatin, lovastatin (used to lower blood cholesterol)
- repaglinide, glyburide (used to treat high blood sugar)
- bosentan (used to treat high blood pressure in the lungs)
- valsartan, olmesartan (used to treat high blood pressure)

Sivextro can interfere with the effects of these medicines. Your doctor will explain more.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or nurse for advice before using this medicine.
It is not known if Sivextro passes into breast milk in humans. Ask your doctor for advice before breast-feeding your baby.

If you are a woman who could become pregnant, you should use reliable contraception while you are taking this medicine. It is currently unknown whether tedizolid phosphate may reduce the effectiveness of birth control pills, skin patches, or certain intrauterine devices, and therefore women using oral birth control pills should add a second barrier method (such as condoms or diaphragm with spermicide). If you become pregnant while you are taking tedizolid phosphate, contact your doctor straight away.

**Driving and using machines**
Do not drive or use machines if you feel dizzy or tired after taking this medicine.

**Sivextro contains sodium**
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e., essentially “sodium-free.”

3. **How you will be given Sivextro**

Sivextro will be given to you by a nurse or doctor.

It will be given to you through a drip directly into a vein (intravenously) over approximately 1 hour.

You will be given one 200 mg infusion of Sivextro once a day for 6 days. Talk to a doctor if you do not feel better, or if you feel worse after 6 days.

**If you are given more Sivextro than you should**
Tell your doctor or nurse immediately if you are concerned that you may have been given too much Sivextro.

**If you miss a dose of Sivextro**
Tell your doctor or nurse immediately if you are concerned that you may have missed a dose.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. **Possible side effects**

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Contact your doctor straight away** if you suffer from diarrhoea during or after your treatment.

**Other side effects may include:**

Common side effects (may affect up to 1 in 10 people)
- Nausea
- Vomiting
- Headache
- Itching all over the body
- Tiredness
- Dizziness
Uncommon side effects (may affect up to 1 in 100 people)
- Fungal infections of skin, mouth and vagina (oral / vaginal thrush)
- Itching (including itching due to allergic reaction), hair loss, acne, red and/or itchy rash or hives, excessive sweating
- Decrease or loss of skin sensitivity, tingling/prickling skin sensation
- Hot flush or blushing/redness in the face, neck or upper chest
- Abscess (swollen, pus-filled lump)
- Vaginal infection, inflammation or itching
- Anxiety, irritability, Shaking or trembling
- Respiratory tract (sinuses, throat and chest) infection
- Dryness in the nose, congestion in the chest, cough
- Sleepiness, abnormal sleep pattern, difficulty sleeping, nightmares (unpleasant/disturbing dreams)
- Dry mouth, constipation, indigestion, pain/discomfort in the belly (abdomen), retching, dry heaving, bright red blood in the stool
- Acid reflux disease (heartburn, pain or difficulty swallowing), flatulence/passing wind,
- Joint pain, muscle spasms, back pain, neck pain, pain/discomfort in limbs, decrease of grip strength
- Blurred vision, ‘floaters’ (small shapes seen floating in the field of vision)
- Swollen or enlarged lymph nodes
- Allergic reaction
- Dehydration
- Poor control of diabetes
- Abnormal sense of taste
- Slow heartbeat
- Fever
- Swelling in ankles and/or feet
- Abnormal smelling urine, abnormal blood tests Infusion site pain or swelling, infusion reactions (chills, shaking or shivering with fever, muscle pain, swelling of the face, weakness, fainting, shortness of breath, chest tightness and angina).

**Reporting of side effects**
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. **How to store Sivextro**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label after “EXP”. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not use this medicine if you notice any particles or the solution is cloudy.

Once opened this medicine must be used immediately. If not, the reconstituted solution should be stored at room temperature for up to 4 hours or in a refrigerator at 2°C to 8°C, for up to 24 hours.

Any unused medicine or waste material, including materials used for reconstitution, dilution and administration, should be disposed of in accordance with local requirements.
6. Contents of the pack and other information

What Sivextro contains

- The active substance is tedizolid phosphate. Each vial of powder contains disodium tedizolid phosphate which is equal to 200 mg of tedizolid phosphate.

- The other ingredients are mannitol, sodium hydroxide (for pH adjustment) and hydrochloric acid (for pH adjustment).

What Sivextro looks like and contents of the pack

Sivextro is a white to off-white powder for concentrate for solution for infusion in a glass vial. The powder will be reconstituted in the vial with 4 ml of water for injections. The reconstituted solution will be withdrawn from the vial and added to an infusion bag of sodium chloride in the hospital.

It is available in packs containing 1 or 6 vials.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Manufacturer

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Italy

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Important: Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Patients who commence treatment on the parenteral formulation may be switched to the oral presentation when clinically indicated.

Sivextro must be reconstituted with water for injections and subsequently diluted in 250 ml of 0.9% sodium chloride for infusion.

Only limited data are available on the compatibility of Sivextro with other intravenous substances, therefore additives or other medicinal products should not be added to Sivextro single use vials or infused simultaneously. If the same intravenous line is used for sequential infusion of several different medicinal products, the line should be flushed before and after infusion with 0.9% sodium chloride. Do not use Lactated Ringer’s Injection or Hartmann’s Solution.
Reconstitution
Aseptic technique must be followed when preparing the infusion solution. Reconstitute the contents of the vial with 4 ml water for injections, and swirl gently until the powder has dissolved entirely. Avoid shaking or rapid movement as it may cause foaming.

Dilution
For administration, the reconstituted solution must be further diluted in 250 ml 0.9% sodium chloride. Do not shake the bag. The resulting solution is a clear colourless or light-yellow solution.

Infusion
The reconstituted solution should be inspected visually for particulate matter prior to administration. Reconstituted solutions containing visible particles should be discarded.

Sivextro is administered intravenously over approximately 1 hour.

The reconstituted solution must be administered as an intravenous infusion only. It must not be administered as an intravenous bolus. Sivextro must not be mixed with other medicinal products.

Each vial is for single use only.