ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Sivextro 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 200 mg tedizolid phosphate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Sivextro is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adults and adolescents 12 years of age and older (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 for adults and adolescents 12 years of age and older 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 below 12 years of age have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology for children below 12 years of age can be made.

Method of administration

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

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Patients with neutropenia

The safety and efficacy of tedizolid phosphate in patients with neutropenia (neutrophil counts <1,000 cells/mm^3) have not been investigated. In an animal model of infection, the antibacterial activity of tedizolid was reduced in the absence of granulocytes. The clinical relevance of this finding is unknown. Alternative therapies should be considered when treating patients with neutropenia and ABSSSI (see section 5.1).

Mitochondrial dysfunction

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

Myelosuppression

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

Peripheral neuropathy and optic nerve disorders

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

Lactic acidosis

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

Hypersensitivity reactions

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

Clostridioides difficile associated diarrhoea

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

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

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

Monoamine oxidase inhibition

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

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of another member of the oxazolidinone class together with serotonergic agents have been reported (see section 4.5).

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

Non-susceptible microorganisms

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

Tedizolid is generally not active against Gram-negative bacteria.

Limitations of the clinical data

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

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

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

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

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

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

Pharmacodynamic interactions

Monoamine oxidase inhibition
Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) *in vitro*; however, no interaction is anticipated when comparing the IC_{50} for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies to determine effects of 200 mg oral tedizolid phosphate at steady state on pseudoephedrine and tyramine pressor effects were conducted in healthy volunteers. No meaningful changes in blood pressure or heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity was observed.

Potential serotonergic interactions
The potential for serotonergic interactions has not been studied in either patients or healthy volunteers (see 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 tedizolid phosphate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Adults
The most frequently reported adverse reactions occurring in patients receiving tedizolid phosphate in the pooled controlled Phase 3 clinical studies (tedizolid phosphate 200 mg once daily for 6 days) were nausea (6.9%), headache (3.5%), diarrhoea (3.2%) and vomiting (2.3%), and were generally mild to moderate in severity.

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

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

Tabulated list of adverse reactions

The following adverse reactions have been identified in two comparative pivotal Phase 3 studies in adults treated with Sivextro (Table 1). Increased ALT, increased AST and liver function tests abnormal were the only adverse drug reactions reported in one comparative Phase 3 study in patients 12 to <18 years of age. Adverse reactions are classified by preferred term and System Organ Class, and by frequency. Frequencies are defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 Adverse reactions by body system and frequency reported in clinical trials and/or post-marketing use

System organ class	Frequency	Adverse reactions
Infections and infestations	*Uncommon:*	Vulvovaginal mycotic infection, fungal infection, vulvovaginal candidiasis, abscess, *Clostridioides difficile* colitis, dermatophytosis, oral candidiasis, respiratory tract infection
Blood and lymphatic system disorders	*Uncommon:*	Lymphadenopathy
	Not known:*	Thrombocytopenia*
Immune system disorders	*Uncommon:*	Drug hypersensitivity
Metabolism and nutrition disorders	*Uncommon:*	Dehydration, diabetes mellitus inadequate control, hyperkalaemia
Psychiatric disorders	*Uncommon:*	Insomnia, sleep disorder, anxiety, nightmare

System organ class	Frequency	Adverse reactions
Nervous system disorders	*Common:* *Uncommon:*	Headache, dizziness Somnolence, dysgeusia, tremor, paraesthesia, hypoaesthesia
Eye disorders	*Uncommon:*	Vision blurred, vitreous floaters
Cardiac disorders	*Uncommon:*	Bradycardia
Vascular disorders	*Uncommon:*	Flushing, hot flush
Respiratory, thoracic and mediastinal disorders	*Uncommon:*	Cough, nasal dryness, pulmonary congestion
Gastrointestinal disorders	*Common:* *Uncommon:*	Nausea, diarrhoea, vomiting Abdominal pain, constipation, abdominal discomfort, dry mouth, dyspepsia, abdominal pain upper, flatulence, gastrooesophageal reflux disease, haematochezia, retching
Skin and subcutaneous tissue disorders	*Common:* *Uncommon:*	Pruritus generalised Hyperhidrosis, pruritus, rash, urticaria, alopecia, rash erythematous, rash generalised, acne, pruritus allergic, rash maculo-papular, rash papular, rash pruritic
Musculoskeletal and connective tissue disorders	*Uncommon:*	Arthralgia, muscle spasms, back pain, limb discomfort, neck pain
Renal and urinary disorders	*Uncommon:*	Urine odour abnormal
Reproductive system and breast disorders	*Uncommon:*	Vulvovaginal pruritus
General disorders and administration site conditions	*Common:* *Uncommon:*	Fatigue Chills, irritability, pyrexia, peripheral oedema
Investigations	*Uncommon:*	Grip strength decreased, transaminases increased, white blood cell count decreased

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

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. Haemodialysis does not result in meaningful removal of tedizolid from systemic circulation. The highest single dose administered in clinical studies was 1,200 mg. All adverse reactions at this dose level were mild or moderate in severity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Tedizolid is primarily active against Gram-positive bacteria.

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

Resistance

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

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

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

Antibacterial activity in combination with other antibacterial and antifungal agents

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

Susceptibility testing breakpoints

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

Organisms	**Minimum Inhibitory Concentrations (mg/L)**	
	Susceptible (≤S)	**Resistant (R>)**
Staphylococcus spp.	0.5	0.5
Beta haemolytic streptococci of Groups A,B,C,G	0.5	0.5
Viridans group streptococci (*Streptococcus anginosus* group only)	0.25	0.25

Pharmacokinetic/pharmacodynamic relationship

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

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

Clinical efficacy against specific pathogens

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

Acute bacterial skin and skin structure infections

- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius* and *S. constellatus*)

Antibacterial activity against other relevant pathogens

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

- *Staphylococcus lugdunensis*

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

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

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

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

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

Special populations

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

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

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

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

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

Drug interaction studies

Effects of other medicines on Sivextro

In vitro studies have shown that drug interactions between tedizolid and inhibitors or inducers of cytochrome P450 (CYP) isoenzymes are unanticipated.

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

Effects of Sivextro on other medicines

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

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

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

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

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

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

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

5.3 Preclinical safety data

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

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

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 $AUC_{0\text{-}24}$ 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 were similar to those in maternal plasma.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose
Mannitol
Povidone
Crospovidone
Magnesium stearate

Film coat

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/991/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2015
Date of latest renewal: 09 January 2020

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.

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 and adolescents 12 years of age and older (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 for adults and adolescents 12 years of age and older 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 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 below 12 years of age have not yet been established. Currently available data are described in section 5.2, but no recommendation on a posology for children below 12 years of age can be made.

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 <1,000 cells/mm^3) have not been investigated. In an animal model of infection, the antibacterial activity of tedizolid was reduced in the absence of granulocytes. The clinical relevance of this finding is unknown. Alternative therapies should be considered when treating patients with neutropenia and ABSSSI (see section 5.1).

Mitochondrial dysfunction

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

Myelosuppression

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

Peripheral neuropathy and optic nerve disorders

Peripheral neuropathy, as well as optic neuropathy sometimes progressing to loss of vision, have been reported in patients treated with another member of the oxazolidinone class with treatment durations exceeding that recommended for tedizolid phosphate. Neuropathy (optic and peripheral) has not been reported in patients treated with tedizolid phosphate at the recommended treatment duration of 6 days. All patients should be advised to report symptoms of visual impairment, such as changes in visual

acuity, changes in colour vision, blurred vision, or visual field defect. In such cases, prompt evaluation is recommended with referral to an ophthalmologist as necessary.

Lactic acidosis

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

Hypersensitivity reactions

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

Clostridioides difficile associated diarrhoea

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

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

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

Monoamine oxidase inhibition

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

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of another member of the oxazolidinone class together with serotonergic agents have been reported (see section 4.5).

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

Non-susceptible microorganisms

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

Tedizolid is generally not active against Gram-negative bacteria.

Limitations of the clinical data

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

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

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

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

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions

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

Pharmacodynamic interactions

Monoamine oxidase inhibitors
Tedizolid is a reversible inhibitor of monoamine oxidase (MAO) *in vitro;* however, no interaction is anticipated when comparing the IC_{50} for MAO-A inhibition and the anticipated plasma exposures in man. Drug interaction studies to determine effects of 200 mg oral tedizolid phosphate at steady state on pseudoephedrine and tyramine pressor effects were conducted in healthy volunteers. No meaningful changes in blood pressure or heart rate with pseudoephedrine were observed in the healthy volunteers, and no clinically relevant increase in tyramine sensitivity was observed.

Potential serotonergic interactions
The potential for serotonergic interactions has not been studied in either patients or healthy volunteers (see 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 tedizolid phosphate therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Adults
The most frequently reported adverse reactions occurring in patients receiving tedizolid phosphate in the pooled controlled Phase 3 clinical studies (tedizolid phosphate 200 mg once daily for 6 days) were nausea (6.9%), headache (3.5%), diarrhoea (3.2%) and vomiting (2.3%), and were generally mild to moderate in severity.

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

Safety was additionally evaluated in a randomised, double-blind, multicenter study conducted in China, the Philippines, Taiwan, and the US, which included a total 292 adult patients treated with tedizolid phosphate 200 mg administered IV and/or oral once daily for 6 days, and 297 patients treated with linezolid 600 mg administered IV and/or oral every 12 hours for 10 days for ABSSSI. The safety profile in this study was similar to the Phase 3 clinical trials; however, infusion site reactions (phlebitis) were reported more frequently (2.7%) in tedizolid phosphate treated subjects than in the linezolid control group (0%), particularly among Asian patients. These findings suggest a higher frequency of infusion related reactions (phlebitis) than was observed in previous clinical studies with tedizolid phosphate.

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

Tabulated list of adverse reactions

The following adverse reactions have been identified in two comparative pivotal Phase 3 studies and one post-authorisation study in adults treated with Sivextro (Table 1). Increased ALT, increased AST and liver function tests abnormal were the only adverse drug reactions reported in one comparative Phase 3 study in patients 12 to <18 years of age. Adverse reactions are classified by preferred term and System Organ Class, and by frequency. Frequencies are defined as: very common (≥1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Table 1 Adverse reactions by body system and frequency reported in clinical trials and/or post-marketing use

System organ class	Frequency	Adverse reactions
Infections and infestations	*Uncommon:*	Vulvovaginal mycotic infection, fungal infection, vulvovaginal candidiasis, abscess, *Clostridioides difficile* colitis, dermatophytosis, oral candidiasis, respiratory tract infection
Blood and lymphatic system disorders	*Uncommon:* *Not known*:*	Lymphadenopathy Thrombocytopenia*
Immune system disorders	*Uncommon:*	Drug hypersensitivity
Metabolism and nutrition disorders	*Uncommon:*	Dehydration, diabetes mellitus inadequate control, hyperkalaemia
Psychiatric disorders	*Uncommon:*	Insomnia, sleep disorder, anxiety, nightmare
Nervous system disorders	*Common:* *Uncommon:*	Headache, dizziness Somnolence, dysgeusia, tremor, paraesthesia, hypoaesthesia
Eye disorders	*Uncommon:*	Vision blurred, vitreous floaters
Cardiac disorders	*Uncommon:*	Bradycardia
Vascular disorders	*Uncommon:*	Flushing, hot flush
Respiratory, thoracic and mediastinal disorders	*Uncommon:*	Cough, nasal dryness, pulmonary congestion
Gastrointestinal disorders	*Common:* *Uncommon:*	Nausea, diarrhoea, vomiting Abdominal pain, constipation, abdominal discomfort, dry mouth, dyspepsia, abdominal pain upper, flatulence, gastrooesophageal reflux disease, haematochezia, retching
Skin and subcutaneous tissue disorders	*Common:* *Uncommon:*	Pruritus generalised Hyperhidrosis, pruritus, rash, urticaria, alopecia, rash erythematous, rash generalised, acne, pruritus allergic, rash maculo-papular, rash papular, rash pruritic
Musculoskeletal and connective tissue disorders	*Uncommon:*	Arthralgia, muscle spasms, back pain, limb discomfort, neck pain
Renal and urinary disorders	*Uncommon:*	Urine odour abnormal
Reproductive system and breast disorders	*Uncommon:*	Vulvovaginal pruritus
General disorders and administration site conditions	*Common:* *Uncommon:*	Fatigue, infusion site reactions (phlebitis) Chills, infusion site pain, irritability, pyrexia, infusion related reaction, peripheral oedema
Investigations	*Uncommon:*	Grip strength decreased, transaminases increased, white blood cell count decreased

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

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. Haemodialysis does not result in meaningful removal of tedizolid from systemic circulation. The highest single dose administered in clinical studies was 1,200 mg. All adverse reactions at this dose level were mild or moderate in severity.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Tedizolid is primarily active against Gram-positive bacteria.

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

Resistance

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

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

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

Antibacterial activity in combination with other antibacterial and antifungal agents

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

Susceptibility testing breakpoints

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

Organisms	Minimum Inhibitory Concentrations (mg/L)	
	Susceptible (≤S)	Resistant (R>)
Staphylococcus spp.	0.5	0.5
Beta haemolytic Streptococci of Groups A,B,C,G	0.5	0.5
Viridans group streptococci (*Streptococcus anginosus* group only)	0.25	0.25

Pharmacokinetic/pharmacodynamic relationship

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

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

Clinical efficacy against specific pathogens

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

Acute bacterial skin and skin structure infections

- *Staphylococcus aureus*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*
- *Streptococcus anginosus* group (including *S. anginosus, S. intermedius* and *S. constellatus*)

Antibacterial activity against other relevant pathogens

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

- *Staphylococcus lugdunensis*

Paediatric population

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

5.2 Pharmacokinetic properties

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

Absorption

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

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

Distribution

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

Biotransformation

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

Elimination

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

Linearity/non-linearity

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

Special populations

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

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

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

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

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

Drug interaction studies

Effects of other medicines on Sivextro

In vitro studies have shown that drug interactions between tedizolid and inhibitors or inducers of cytochrome P450 (CYP) isoenzymes are unanticipated.

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

Effects of Sivextro on other medicines

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

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

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

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

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

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

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

5.3 Preclinical safety data

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

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

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 $AUC_{0\text{-}24}$ 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., Ca^{2+}, Mg^{2+}), including Lactated Ringer’s Injection and Hartmann's Solution.

6.3 Shelf life

3 years.

The combined storage time (from reconstitution to dilution to administration) must not exceed 24 hours when stored at either room temperature or in a refrigerator (2°C - 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 the vial 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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 March 2015
Date of latest renewal: 09 January 2020

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.

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

FAREVA Mirabel
Route de Marsat, Riom
63963, Clermont-Ferrand Cedex 9
France

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 (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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 marketing authorisation holder (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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

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

Film-coated tablet
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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/991/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Sivextro

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

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

MSD

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Peel, then push

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (VIAL)

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains disodium tedizolid phosphate corresponding to 200 mg tedizolid phosphate.
After reconstitution each mL contains 50 mg tedizolid phosphate.

3. LIST OF EXCIPIENTS

mannitol, sodium hydroxide, hydrochloric acid

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial
6 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Intravenous use after reconstitution and dilution
For single use only

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

Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

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

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Sivextro 200 mg powder for concentrate
tedizolid phosphate
IV

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Sivextro 200 mg film-coated tablets
tedizolid phosphate

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

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 and adolescents 12 years of age and older 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).
- have a history of bleeding or easy bruising (which may be a sign of low numbers of platelets, the small cells involved in clotting in your blood).
- have kidney problems.
- are taking certain medicines to treat depression, known as tricyclics, SSRIs (selective serotonin reuptake inhibitors) or MAOIs (monoamine oxidase inhibitors). See Other medicines and Sivextro for examples.
- are taking certain medicines to treat migraine known as "triptans". See Other medicines and Sivextro for examples.

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.

Possible side effects
Certain side effects have been observed with Sivextro or 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
This medicine should not be used in children under 12 years of age as it has not been studied enough in this population.

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:
- amitriptyline, citalopram, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, isocarboxazid, lofepramine, moclobemide, paroxetine, phenelzine, selegiline and sertraline (used to treat depression)
- sumatriptan, zolmitriptan (used to treat migraine)
- imatinib, lapatinib (used to treat cancer)
- methotrexate (used to treat cancer, rheumatoid arthritis or psoriasis)
- sulfasalazine (used to treat inflammatory bowel diseases)
- topotecan (used to treat cancer)
- statins such as pitavastatin, rosuvastatin (used to lower blood cholesterol)

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.

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

Frequency not known (frequency cannot be estimated from the available data)
- Bleeding or bruising easily (due to low numbers of platelets, the small cells involved in clotting in your blood)

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.

Marketing Authorisation Holder
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Manufacturer
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63963, Clermont-Ferrand Cedex 9
France

Merck Sharp & Dohme B.V.
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2031 BN Haarlem
The Netherlands

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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

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

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 and adolescents 12 years of age and older 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 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) being treated with antibiotics in the past.
- are allergic to other medicines belonging to the group "oxazolidinones" (e.g., linezolid, cycloserine).
- have a history of bleeding or easy bruising (which may be a sign of low numbers of platelets, the small cells involved in clotting in your blood).
- have kidney problems.
- are taking certain medicines to treat depression, known as tricyclics, SSRIs (selective serotonin reuptake inhibitors) or MAOIs (monoamine oxidase inhibitors). See Other medicines and Sivextro for examples.
- are taking certain medicines to treat migraine known as "triptans". See Other medicines and Sivextro for examples.

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.

Possible side effects
Certain side effects have been observed with Sivextro or 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
This medicine should not be used in children under 12 years of age as it has not been studied enough in this population.

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:
- amitriptyline, citalopram, clomipramine, dosulepin, doxepin, fluoxetine, fluvoxamine, imipramine, isocarboxazid, lofepramine, moclobemide, paroxetine, phenelzine, selegiline and sertraline (used to treat depression)
- sumatriptan, zolmitriptan (used to treat migraine)

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.

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

Sivextro contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say 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
- Infusion site pain or swelling.

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 reactions (chills, shaking or shivering with fever, muscle pain, swelling of the face, weakness, fainting, shortness of breath, chest tightness and angina pectoris).

Frequency not known (frequency cannot be estimated from the available data)
- Bleeding or bruising easily (due to low numbers of platelets, the small cells involved in clotting in your blood)

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 and diluted solution should be stored at room temperature or in a refrigerator at 2°C to 8°C, and administered within 24 hours after reconstitution.

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 0.9% 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
Merck Sharp & Dohme B.V.
Waarderweg 39
2031 BN Haarlem
The Netherlands

Manufacturer
FAREVA Mirabel
Route de Marsat, Riom
63963, Clermont-Ferrand Cedex 9
France

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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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.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for tedizolid phosphate, the scientific conclusions of CHMP are as follows:

In view of available data on thrombocytopenia from the literature and spontaneous reports, including 10 cases medically confirmed with a close temporal relationship and three possible positive de-challenges, the PRAC considered a causal relationship between tedizolid phosphate and thrombocytopenia is at least a reasonable possibility. Additionally, in 9 out of the 10 cases the event occurred with therapies longer than those recommended in the SmPC (6 days) and in 5 cases renal impairment was present (4 chronic of which 2 were in dialysis, and 1 acute renal impairment). The PRAC concluded that the product information of products containing tedizolid phosphate should be amended as follows:

Update section 4.4 of the SmPC to include that patients with renal impairment and those who receive treatment for longer than recommended are at higher risk to develop the event of thrombocytopenia and add a recommendation to minimise the risk.

Update of section 4.8 of the SmPC to add the adverse reaction thrombocytopenia under the frequency "unknown".

The Package leaflet is updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for tedizolid phosphate the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing tedizolid phosphate is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.