EU RISK MANAGEMENT PLAN (RMP) FOR

tedizolid phosphate

200 mg film-coated tablets

200 mg powder for concentrate for solution for infusion

20 mg/mL powder for oral suspension

RMP version to be assessed as part of this application:

RMP Version number: 9.0

Data lock point for this RMP: 20-JUN-2025

Date of finalization: 17-JUN-2026

Rationale for submitting an updated RMP:

This EU RMP is updated with the submission of a new formulation, the powder for oral suspension.

Summary of significant changes in this RMP:

RMP Section	UPDATE INFORMATION
PART I: PRODUCT(S) OVERVIEW	Powder for oral suspension formulation and indication added
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)	Epidemiology information updated
PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE	Results of P044 added Patient exposure data from clinical studies updated Former company safety database name removed
PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE	Postmarketing patient exposure data updated
PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT	Powder for oral suspension formulation added

Other RMP versions under evaluation: Not applicable

Details of the currently approved RMP:

Version number: 8.0

Approved with procedure: EMEA/H/C/002846/II/0054

Date of approval (CHMP Opinion date): 30-JAN-2025

Qualified Person for Pharmacovigilance (QPPV) name: Peter de Veene, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Experience
ATC	Anatomical Therapeutic Chemical classification system
ATMP	Advanced Therapy Medicinal Product
BID	Twice A Day
BSI	Bloodstream infections (bacteraemia)
CCDS	Company Core Data Sheet
CCSI	Company Core Safety Information
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralized Procedures – Human
CT	Computed Tomography
DILI	Drug Induced Liver Injury
DUS	Drug Utilization Study
ECG / EKG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPITT	European Pharmacovigilance Issues Tracking Tool
EU	European Union
HAI	Healthcare Associated Infection
HGB	Hemoglobin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Council for Harmonization
IM	Intramuscular(ly)
INN	International Nonproprietary Name
IV	Intravenous(ly)
MAA	Marketing Authorization Applicant
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimum Inhibitory Concentration
MRI	Magnetic Resonance Imaging
MRSA	Methicillin-resistant *Staphylococcus aureus*
MSSA	Methicillin-susceptible *Staphylococcus aureus*
N/A	Not Applicable
PAES	Post-authorization Efficacy Study

PASS	Post-authorization Safety Study
PFOS	Powder for oral suspension
PO	Oral(ly)
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PT	Preferred Term
QD	Once Daily
QOD	Every Other Day
QPPV	Qualified Person for Pharmacovigilance
QWK	Once Weekly
RMP	Risk Management Plan
SC	Subcutaneous
SOC	System Organ Class
SmPC	Summary of Product Characteristics
SSSI	Skin and skin structure infections
STAR	Surveillance of Tedizolid Activity and Resistance Program.
TIW	Three Times Per Week
WBC	White Blood Cell Count

PART I: PRODUCT(S) OVERVIEW

Table I.1: Product Overview

Active substance(s)	Tedizolid phosphate
Pharmacotherapeutic group(s) (ATC Code)	Oxazolidinone antibiotic / Antibacterials for systemic use, Other antibacterials (J01XX11)
Marketing Authorisation Holder or Applicant	Merck Sharp & Dohme B.V.
Number of medicinal products to which this RMP refers	3
Invented name(s) in the European Economic Area (EEA)	Sivextro 200 mg film-coated tablets Sivextro 200 mg powder for concentrate for solution for infusion Sivextro 20 mg/mL powder for oral suspension
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical Class: Oxazolidinone antibiotic
	Tedizolid phosphate, the free acid prodrug form, is an oxazolidinone antibiotic that is rapidly converted in vivo by phosphatases to the microbiologically active moiety, tedizolid.
Hyperlink to the Prescribing Information	Proposed EU-product information: [Ref. 1.3.1: ema-combined-h2846-en-wrm.pdf] Current approved EU-product information: [Ref. 1.3.1: ema-combined-h2846-en-crt.pdf] (EMEA/H/C/002846/II/0054; CHMP Opinion: 30 January 2025)
Indication(s) in the EEA	Current Sivextro powder for concentrate for solution for infusion is indicated for the treatment of acute bacterial skin and soft structure infections (ABSSSI) from birth. Sivextro film-coated tablets are indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult, adolescents and children weighing at least 35 kg.
	Proposed addition: Sivextro powder for oral suspension: Sivextro powder for oral suspension is indicated for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in patients from birth.

Table I.1: Product Overview

<table>
<tr>
<td>Dosage in the EEA</td>
<td>
For the film-coated tablets:
The recommended dosage for adults, as well as adolescents and children weighing at least 35 kg is 200 mg once daily for 6 days.
Tedizolid phosphate tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral presentation when clinically indicated.

For the powder for concentrate for solution for infusion:
• Adults, as well as adolescents and children weighing at least 35 kg
The recommended dosage of tedizolid phosphate is 200 mg once daily for 6 days. Tedizolid phosphate tablets or powder for concentrate for solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to the oral presentation when clinically indicated.

• Adolescents and children weighing less than 35 kg
The recommended intravenous dosage of tedizolid phosphate is presented in Table 1. In these patients, tedizolid phosphate is administered twice daily for 6 days, as an IV infusion over 1 hour.

Table 1: Intravenous dosage of tedizolid phosphate for paediatric patients weighing less than 35 kg
<table>
<tr><th>Weight Band (kg)</th><th>Dosage</th><th>Frequency</th></tr>
<tr><td>1 to less than 3</td><td>6 mg</td><td>Twice daily</td></tr>
<tr><td>3 to less than 6</td><td>12 mg</td><td>Twice daily</td></tr>
<tr><td>6 to less than 10</td><td>20 mg</td><td>Twice daily</td></tr>
<tr><td>10 to less than 14</td><td>30 mg</td><td>Twice daily</td></tr>
<tr><td>14 to less than 20</td><td>40 mg</td><td>Twice daily</td></tr>
<tr><td>20 to less than 35</td><td>60 mg</td><td>Twice daily</td></tr>
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Table I.1: Product Overview

Proposed:

Tedizolid phosphate tablets, powder for oral suspension 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 an oral presentation when clinically indicated.

For the film-coated tablets:

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

For the powder for concentrate for solution for infusion:

- *Adults, as well as adolescents and children weighing at least 35 kg*

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

- *Adolescents and children weighing less than 35 kg*

The recommended intravenous dosage of tedizolid phosphate is presented in Table 1. In these patients, tedizolid phosphate is administered twice daily for 6 days, as an IV infusion over 1 hour.

Table 1: Intravenous dosage of tedizolid phosphate for paediatric patients weighing less than 35 kg

Weight Band (kg)	Dosage	Frequency
1 to less than 3	6 mg	Twice daily
3 to less than 6	12 mg	Twice daily
6 to less than 10	20 mg	Twice daily
10 to less than 14	30 mg	Twice daily
14 to less than 20	40 mg	Twice daily
20 to less than 35	60 mg	Twice daily

For the powder for oral suspension:

- *Adults, as well as adolescents and children weighing at least 35 kg*

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

- *Adolescents and children weighing less than 35 kg*

The recommended dosage of tedizolid phosphate is presented in Table 1. In these patients, tedizolid phosphate is administered twice daily for 6 days.

Table 1: Dosage of tedizolid phosphate for paediatric patients weighing less than 35 kg

Weight Band (kg)	Dosage	Frequency
1 to less than 3	6 mg	Twice daily
3 to less than 6	12 mg	Twice daily
6 to less than 10	20 mg	Twice daily
10 to less than 14	30 mg	Twice daily
14 to less than 20	40 mg	Twice daily
20 to less than 35	60 mg	Twice daily

Table I.1: Product Overview

Pharmaceutical form(s) and strengths	Yellow film-coated tablet containing 200 mg tedizolid phosphate. Vial of white to off-white lyophilised powder for concentrate for solution for infusion containing disodium tedizolid phosphate corresponding to 200 mg tedizolid phosphate. Oral Suspension is supplied as a powder for oral suspension in a single-use packet containing 245.3 mg tedizolid phosphate to be constituted with water to form a suspension.
Is/will the product be subject to additional monitoring in the EU?	No

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indication: Acute Bacterial Skin and Skin Structure Infections (ABSSSI)

Incidence:

The overall global incidence of ABSSSI, a more severe subset of skin and soft tissue infections (SSTI's), is not well described. However, skin and skin structure infections are very common, frequently encountered in both community and hospital settings, and are common causes of presentation to emergency departments. A study utilizing administrative claims data from 14 health plans in the US from 2005-2010 found that an overall incidence of SSTI ranged from 42.85 to 51.23 per 1,000 person-years in the ambulatory setting; while in the inpatient setting, incidence ranged from 0.91 to 3.87 per 1,000 person-years, for patients aged 0-64 years [Ref. 5.4: 04R388]. The incidence in the paediatric population (0-17 years) was 43.51 (95% CI: 43.40, 43.63) per 1,000 person-years in the ambulatory setting and 0.91 (95%CI: 0.89, 0.93) in the inpatient setting [Ref. 5.4: 04R388]. A retrospective study using a nationwide claims database in the US from 2010-2020, analyzed 9.1 million SSTI episodes and reported an SSTI incidence rate of 77.5 (95% CI: 77.4-77.5) per 1,000 person-years, with no significant change in annual incidence over time [Ref. 5.4: 08TSMX]. In addition, a US study found that the incidence of SSTI among all patients in 2014 was 29.7 per 1,000 emergency department encounters [Ref. 5.4: 04ZHQJ].

The incidence of ABSSSI in children is not well characterized. In an effort to evaluate current epidemiology trends, an analysis was conducted using a US-based electronic insurance claims database (Merative MarketScan) to estimate the annual age-specific incidence of first ABSSSI in children 0 to <18 years of age. ABSSSI including cellulitis/erysipelas, major cutaneous abscess, and wound infection [Ref. 5.4: 04R2BF] makes up the majority of SSTI resulting in healthcare claims [Ref. 5.4: 04H0JY, 04R388]. All physician office, emergency department, and hospital encounters occurring between1 January 2005 and 31 December 2015 with a first ABSSSI diagnosis were identified (per patient per year). An ABSSSI diagnosis was defined as cellulitis, abscess, post-operative infection, carbuncle, post-trauma wound infection, erysipelas, or orbital cellulitis, per International Classification of Disease, 9th Revision (ICD-9) codes. Over the 11 years, there were 2,144,959 ABSSSI episodes identified, and the majority (96%) were diagnosed in the ambulatory setting. In 2015, the overall incidence was highest in the 12 to <18-year age group (16.80 per 1,000 patients), followed by the 2 to <12-year age group (14.50 per 1,000 patients) and 0 to <2-year age group (13.64 per 1,000 patients). The incidence in the inpatient setting was considerably lower; 1.31, 0.38 and 0.47 per 1,000 patients in the 0 to <2-year group, 2 to <12 -year group and 12 to <18-year group, respectively. An updated analysis of this claims database found that the annual incidence of ABSSSI was generally comparable across age groups except for infants <1 year of age. From 2012 to 2019, the annual incidence of ABSSSI was lower in infants <1 year of age compared with other paediatric age groups: birth to <1 year (15 to 17 cases/1000 person-years), 1 to <2 years (22 to 27 cases/1000 person-years), 2 to <6 years (23 to 26 cases/1000 person-years), 6 to <12 years (20 to

23 cases/1000 person-years), and 12 to <18 years (23 to 29 cases/1000 person-years) [Ref. 5.4: 08VR9K].

Staphylococcus aureus (S. aureus), predominately methicillin-resistant strains, are a major cause of SSTI worldwide [Ref. 5.4: 04BWFW, 08JY84]. Methicillin-resistant *Staphylococcus aureus* (MRSA) infections are estimated to affect 150,000 patients per year in the EU [Ref. 5.4: 04BWFW]. The rate of surgical site infections per 100 surgical procedures in Europe varies from 0.6% following knee prosthesis surgery to 9.5% following colon surgery; the majority of surgical site infections were due to gram-positive pathogens, and *S. aureus* was one of the most commonly reported microorganisms [Ref. 5.4: 08L7ZD].

Prevalence:

According to a review of the burden of MRSA in Europe, MRSA was estimated to account for 44% of all reported HAIs [Ref. 5.4: 04BWFW]. Data from the European Antimicrobial Resistance Surveillance (EARS) Network suggest that the population-weighted average MRSA prevalence in tested isolates ranged from 15.7% to 16.9% from 2017 to 2021; however, these rates varied largely by country, ranging from 0.9%-42.9% in 2021 [Ref. 5.4: 08L7Z0]. In paediatric patients, the reported rate of MRSA in isolates was greater than 50%; therefore, children are included among the categories with a higher risk of community-acquired MRSA infection together with military personnel, prisoners, athletes, people who inject drugs and those institutionalized, or with frequent healthcare contact [Ref. 5.4: 08JY84].

Demographics of the Adult Population in the Authorised Indication and Risk Factors for the Disease:

Skin infections can occur in any age group, but the risk for invasive gram-positive infections (ABSSSIs with bacteraemia, joint or bone involvement) increases in patients with certain medical conditions and lifestyle choices including: diabetes mellitus, lymphedema, severe renal insufficiency requiring haemodialysis, peritoneal dialysis, injection drug use, alcohol abuse, or presence of tattoos and/or body piercings. Recent community-acquired MRSA outbreaks have also been reported in people who engage in contact sports, incarcerated adults, and in military recruits [Ref. 5.4: 044M4P].

In a multinational, multicentre, observational, retrospective cohort study conducted in Europe among 1,995 patients with cSSTI (REACH), approximately 45% of the hospitalised patients were elderly (age >65 years), 78% of patients had some clinical co-morbidity at the time of admission to the hospital for treatment of their infection, and approximately 21% had been hospitalised within 3 months prior to the episode of the cSSTI [Ref. 5.4: 04BWDW].

Demographics of the Paediatric Population in the Proposed Indication and Risk Factors for the Disease:

In the paediatric population, the overall incidence was highest in the 12 to less than 18-year age group (16.80 per 1,000 patients), followed by the 2 to < 12-year age group (14.50 per 1,000 patients) and 0 to < 2-year age group (13.64 per 1,000 patients). An updated analysis resulted in comparable incidence across paediatric age groups except for infants <1 year of

age: birth to <1 year (15 to 17 cases/1000 person-years), 1 to <2 years (22 to 27 cases/1000 person-years), 2 to <6 years (23 to 26 cases/1000 person-years), 6 to <12 years (20 to 23 cases/1000 person-years), and 12 to <18 years (23 to 29 cases/1000 person-years) (data on file). More than 95% of cases are in the ambulatory setting. However, in the inpatient setting, the incidence is much lower but highest in the 0-2-year age group; 1.31, 0.38 and 0.47 per 1,000 patients in the 0 to < 2-year group, 2 - <12 -year group and 12 to less than 18- year group, respectively (these results are based on an internal analysis of Merative MarketScan data in the US).

The Main Existing Treatment Options:

Antibiotics are the mainstay for treatment of ABSSSI. Depending on the infection other measures could include drainage. The main treatment options recommended by consensus guidelines for treatment of cSSTIs/ABSSSIs include beta lactams (nafcillin, oxacillin, or dicloxacillin; cefazolin or cephalexin) for infections involving methicillin-susceptible *S. aureus* (MSSA) or pathogenic streptococci, and vancomycin, clindamycin, linezolid, doxycycline, trimethoprim-sulfamethoxazole, and daptomycin for MRSA infections.

Natural History of the Indicated Condition in the Population, Including Mortality and Morbidity:

Potential complications of ABSSSIs include sepsis, bacteraemia, secondary spread of the infection through the bloodstream to other sites, or direct contiguous spread to involve bone or joints (invasive infections). A recent review suggests widely varying MRSA mortality rates that range from 10-64% [Ref. 5.4: 04BWFW]. A survey of MRSA infections in the US found mortality rates of 6.1% and 10.2% among patients with cellulitis and patients with bacteraemia respectively [Ref. 5.4: 044M4M]. A retrospective study using a nationwide claims database in the US reported that deaths occurring within 30 days post–SSTI hospitalization rose from 2.6% in 2010 to 4.6% in 2020 [Ref. 5.4: 08TSMX].

Important Co-Morbidities:

- Diabetes
- Immunological disorders
- Hepatic disease
- Obesity

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Table SII.1: Summary of Important Safety Findings From Non-clinical Studies

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Repeat Dose Toxicity Haematological findings: The haematopoietic system was a target organ in rats following PO and IV repeat dose administration of tedizolid phosphate, with these effects showing evidence of reversibility and occurring at many multiples of the human tedizolid therapeutic exposure level. Haematopoietic effects after chronic (28-day and 3-month) oral administration in rats were characterised by 1) mild-moderate changes in circulating RBC, WBC, and platelets; 2) myeloid, erythroid, and megakaryocyte hypocellularity in bone marrow; and 3) decreased splenic B cells. In dogs no toxicologically relevant changes in haematology parameters were observed after oral administration. Changes in haematology indicative of myelosuppression were seen in rats after IV administration, although no bone marrow histological changes were reported. In dogs, hypocellularity in bone marrow was seen in one dog after IV administration at doses higher than the equivalent human 200 mg exposure (based on plasma $AUC_{0\text{-}24hr}$ levels). Safety margins based on comparison of tedizolid plasma $AUC_{0\text{-}24hr}$ levels identified at the NOAELs and at the therapeutic dose in humans ranged from 3.7- to 7.4-fold in the 28-day, 3-month, and 9-month studies conducted in rats. In dogs, safety margins ranged from ≥3.0- to ≥6.8-fold in the 28-day and 3-month dog studies. Systemic safety margins, based on tedizolid plasma $AUC_{0\text{-}24hr}$ levels in the 28-day rat and 14-day dog IV studies relative to the human therapeutic plasma exposure, were 4.3-fold for male and 3.3-fold for female rats and 3.1-fold for male and 3.2-fold for female dogs.	In clinical studies in healthy volunteers, tedizolid phosphate was associated with dose- and time-dependent effects on the haematology laboratory assessments at dose exposures higher than 200 mg daily for treatment periods up to 21 days. Clinically significant decreases in haematologic parameters (ie, clinically substantial decreases in platelets, red and white blood cell counts) remain potential dose-limiting adverse reactions, particularly for dosing oxazolidinones over extended periods of time or at higher doses.

Table SII.1: Summary of Important Safety Findings From Non-clinical Studies

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Repeat Dose Toxicity Hepatic findings: Hepatic findings were observed in the rat 3-month tedizolid phosphate oral toxicity study at high doses that were poorly tolerated (including mortality). Hepatocellular centrilobular degeneration and atrophy was accompanied by plasma elevations in alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyltransferase (GGT). Tedizolid phosphate was not associated with adverse hepatic effects in rats at exposure margins of 4.8-fold relative to tedizolid plasma AUC_{last} levels at the human oral therapeutic dose. Hepatic changes were not seen in the dog 3-month study and showed evidence of reversibility in rats.	There were no safety signals for hepatic toxicity observed in Phase 1, 2, and 3 clinical trials with tedizolid phosphate at the proposed clinical dose. Transaminase (ALT, AST) and total bilirubin values were screened for any evidence of drug induced serious hepatotoxicity (DISH) using Hy's Law laboratory criteria (ALT or AST > 3 times the upper limit of normal [ULN] plus TBIL >2 times ULN). There was no DISH signal in the integrated safety database from pooled Phase 2/3 clinical trials in ABSSSI patients. Increased ALT, AST or GGT levels were reported as treatment related adverse events (TRAEs) in 2.9%, 2.4%, and 1.3% of tedizolid-treated patients in Phase 3 clinical trials (N=1037). None of these TRAEs were serious and none of the events led to treatment discontinuation. Therefore, hepatic toxicity is not identified as an important potential risk of tedizolid phosphate.
Repeat Dose Toxicity Reproductive organ findings: Reproductive organ findings were observed in the rat 3-month tedizolid phosphate oral toxicity study at high doses that were poorly tolerated, resulting in early euthanasia of morbid/moribund animals. Degeneration and atrophy of hormone-sensitive reproductive organs (testes, male accessory glands, ovaries, uterus, vagina, and cervix) were observed at these doses. Tedizolid phosphate was not associated with adverse effects in rats at exposure margins of ≥5.3-fold for males and ≥4.2-fold for females relative to tedizolid plasma $AUC_{0\text{-}24hr}$ levels at the human oral therapeutic dose. Changes in reproductive organs were not seen in the dog 3-month study and showed evidence of reversibility in rats. 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.	There are no data from well controlled trials studying the use of tedizolid in pregnant women. As a precautionary measure; it is preferable to avoid the use of tedizolid during pregnancy.

Table SII.1: Summary of Important Safety Findings From Non-clinical Studies

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Reproductive and developmental toxicity: **Fertility:** Tedizolid phosphate had no adverse effects on the fertility or reproductive performance of female rats at oral doses up to 15 mg/kg/day (NOAEL; highest dose) tested or male rats at oral doses up to 50 mg/kg/day (NOAEL; highest dose tested). Systemic exposure (AUC) at these NOAELs are >5.3-fold (male) and >4.2-fold (female) higher than that in humans given 200 mg once daily. No adverse effects on spermatogenesis were observed. **Embryo-foetal toxicity:** 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. **Pre- and post-natal toxicity:** No adverse effects on offspring growth, maturation or measures of neurobehavioral or reproductive function were observed in rats with oral administration of tedizolid phosphate. The tedizolid plasma AUC_{0-24} level estimated for the highest tested dose in this study was also comparable to the human oral therapeutic plasma exposure. Tedizolid exposure to foetuses was confirmed; with mean plasma foetal concentrations approximately 24%-37% of maternal plasma at 2 hours following administration of tedizolid phosphate. Similarly, the F_1 offspring which were exposed to tedizolid as lactating rats showed similar concentrations in milk and plasma.	Studies in mice and rats showed developmental effects which are included in Section 5.3. of the SmPC. There are no data from the use of tedizolid in pregnant women. As a precautionary measure, it is preferable to avoid the use of tedizolid during pregnancy. It is unknown whether tedizolid or its metabolites are excreted in human milk. Tedizolid is excreted in the breast milk of rats. 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 therapy takinginto account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Table SII.1: Summary of Important Safety Findings From Non-clinical Studies

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
General safety pharmacology:	
Nervous system: Ten studies of tedizolid phosphate, given as single oral doses up to 100 mg/kg, were conducted in rodents to evaluate the effects on general behaviour, locomotor activity, motor coordination, body temperature, pain response, and sleep. No toxicologically meaningful changes were observed in the neurobehavioral assessments. Three studies were conducted to evaluate the effect of tedizolid phosphate on convulsions in mice induced by electrical shock, pentylene-tetrazole, and strychnine. There were no treatment-related effects on convulsions.	There were no signals indicative of neurotoxicity observed in Phase 1, 2, and 3 clinical trials with tedizolid phosphate at the proposed clinical dose and duration of 6 days. In Phase 3 trials, reported adverse reactions for peripheral neuropathy and optic nerve disorders identified by a standardised MedDRA query were similar between both treatment arms (peripheral neuropathy 1.2% vs. 0.6% for tedizolid phosphate and linezolid, respectively; optic nerve disorders 0.3% vs. 0.2%, respectively). No data are available for patients exposed to tedizolid phosphate for longer than 6 days. Tedizolid phosphate was administered in two healthy volunteers for up to 3 weeks at up to twice the therapeutic dose. No evidence of peripheral neuropathy and optic neuropathy was found. However, neurotoxicity with prolonged use of linezolid has been identified as a potential risk. Peripheral and optic neuropathies are categorised as potential risks for prolonged use of tedizolid phosphate based on published post-marketing experience with linezolid.
Mechanisms for drug interactions • **Monoamine oxidase (MAO) inhibition:** Tedizolid was found to be a reversible inhibitor of MAO_A and MAO_B *in vitro*. Potent MAO_A inhibitors can produce increased blood pressure when co administered with sympathomimetic agents, or after dietary intake of tyramine-rich foods. • **Tyramine:** Two *in vivo* tyramine challenge studies were conducted in rats to assess the significance of the *in vitro* MAO enzyme inhibition of tedizolid (inactive prodrug tedizolid phosphate was found to have no *in vitro* MAO inhibition). In rats at doses up to 150 mg/kg (33-fold above anticipated human exposures at the therapeutic dose of 200 mg daily), oral tedizolid phosphate did not induce a hypertensive pressor response, suggesting a tyramine interaction in humans is unlikely. In contrast linezolid (50 mg/kg), at doses comparable to exposure levels achieved in humans at its therapeutic dose, induced a positive tyramine pressor response. • **Serotonin:** A mouse model of serotonergic activity showed that, unlike linezolid (a selective MAO_A inhibitor) and selective serotonin reuptake inhibitors (SSRIs), tedizolid phosphate did not display an increase in head twitch, a marker for brain serotonin activity.	No interaction is anticipated based on a high therapeutic index for MAO inhibition when comparing IC_{50} and the anticipated tedizolid plasma exposures (C_{max}) in man. No dietary restrictions on tyramine intake appear warranted and no clinically important interactions with sympathomimetics are anticipated. Drug interaction studies to determine effects of 200 mg oral tedizolid at steady state on pseudoephedrine and tyramine pressor effects have been conducted. No meaningful changes in blood pressure and heart rate with pseudoephedrine and no clinically relevant increase in tyramine sensitivity were observed. The risks for serotonin syndrome and hypertensive crises during use of tedizolid are considered to be low. No clinically important interactions with serotonergic drugs are anticipated based on the mouse study. Prescribers will be informed of the results of the mouse study in Section 5.2 of the SmPC and be advised that serotonergic drugs, contraindicated for the comparator drug linezolid, were excluded from the tedizolid clinical studies.

Table SII.1: Summary of Important Safety Findings From Non-clinical Studies

Key Safety Findings (From Non-clinical Studies)	Relevance to Human Usage
Other toxicity-related information or data- **Miscellaneous effects associated with off target effects of ribosomal binding seen with linezolid:** Adverse effects associated with linezolid that were considered potential risks for tedizolid phosphate included peripheral and optic neuropathy, convulsions, and lactic acidosis. A repeat dose 9-month neuropathology study was conducted with tedizolid phosphate in pigmented rats addressing functional and histopathological neurotoxicity endpoints. This study had histopathological evaluations at 1, 3, 6 (with a 3 month recovery group after 6 months of treatment), and 9 months, and used special stains and sensitive microscopic techniques. Tissues assessed included brain, eyes (includes retina and uveal tract), optic tract/nerves, spinal cord, peripheral ganglia/nerves (includes sciatic nerve), and skeletal muscle. No tedizolid phosphate induced functional observational changes or histopathological effects were seen in this study at plasma tedizolid exposures that averaged 5.8-fold (approximately 8-fold at 9 months) over the therapeutic human plasma exposure. Three studies were conducted to evaluate the effect of tedizolid phosphate on convulsions in mice induced by electric shock, pentylene-tetrazole and strychnine. There were no treatment-related effects on convulsions. There are no data available to characterize the risk potential for lactic acidosis from non-clinical assessments.	The nonclinical studies with tedizolid did not find evidence of optic or peripheral neuropathic lesions. These adverse reactions are typically associated with prolonged use of linezolid (>28 days), and therefore unlikely to occur over the short 6-day duration of therapy proposed for clinical use of tedizolid phosphate in ABSSSI.

Conclusions on Non-clinical Data

The following safety concerns reflect the conclusions based on the findings in non-clinical studies with tedizolid phosphate.

Table SII.2: Non-clinical Safety Concerns

Important identified risks
Myelosuppression (eg, decreased platelets, decreased haemoglobin, decreased neutrophils): Tedizolid phosphate was associated with dose-dependent effects on the haematopoietic system (decreased bone marrow cellularity) at the highest exposures in rat toxicology studies, and there was reversal of changes after the drug-free recovery phase. In clinical studies in healthy volunteers, tedizolid phosphate was associated with dose- and time-dependent effects on the haematology laboratory assessments at dose exposures higher than 200 mg daily for treatment periods up to 21 days.
Important potential risks (not refuted by clinical data or which are of unknown significance)
Serotonin syndrome: From *in vitro* assessments of potential off-target pharmacological activity of tedizolid conducted with biochemical, enzyme, and radioligand binding assays, the only noteworthy finding was a reversible inhibition of MAO_A and MAO_B. Potent MAO_A inhibitors can produce serotonin syndrome when co-administered with serotonergic agents. The maximum free tedizolid plasma concentration at the proposed clinical dose was 0.2 times below the IC50 for MAO inhibition. No serotonergic effects were observed with tedizolid in a mouse head twitch model, which suggests that interactions with serotonergic agents in humans are unlikely. However, as serotonergic drugs were contraindicated for the comparator drug linezolid, patients receiving these medicinal products were excluded from tedizolid clinical trials. Thus, there is no clinical evidence to evaluate risk from concurrent use of tedizolid phosphate with serotonergic agents in humans.
Peripheral and optic nerve toxicity, lactic acidosis: As bacterial protein synthesis inhibitors, oxazolidinones have the potential for off-target effects mediated through inhibition of mitochondrial protein synthesis due to similarities in the binding sites on mitochondrial ribosomal subunits. Retrospective reviews of postmarketing cases of prolonged used of linezolid have associated optic and peripheral neuropathies, as well as lactic acidosis, with inhibition of mitochondrial protein synthesis with a potential genetic predisposition [Ref. 5.4: 0492QW]. In a thorough and detailed assessment of the neuropathic potential of tedizolid phosphate in rats, no evidence was found of optic and peripheral neuropathic lesions at systemic exposures equivalent to up to 8-fold those observed in human at the therapeutic dose of 200 mg once daily. As the dose regimens tested in Phase 2/3 clinical trials to date have been ≤ 7 days, there is no clinical evidence to confirm or refute this potential risk.
Missing information
Pregnancy and Lactation: There are no data from the use of tedizolid in pregnant women. Tedizolid was not teratogenic in mice or rats at exposure levels approximately 4-fold (in mice) and 6-fold (in rats) higher than the human exposure levels with 200 mg tedizolid phosphate daily. In embryo-foetal studies, tedizolid phosphate was shown to produce foetal developmental toxicities in mice and rats. The no observed adverse effect levels (NOAELs) for foetal toxicity in mice as well as maternal and foetal toxicity in rats 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. No adverse effects were observed in rat pups when exposed to tedizolid via ingestion of milk during lactation. Tedizolid is excreted in the breast milk of rats. It is not known whether tedizolid is excreted in human milk.

See also Part II Module SVIII: Summary of Safety

Table SII.3: Summary of Important Safety Concerns From Non-clinical Data

Important identified risks	• Myelosuppression (eg, decreased platelets, decreased haemoglobin, decreased neutrophils)
Important potential risks	• Serotonin syndrome • Peripheral and optic nerve toxicity • Lactic acidosis
Missing information	• Pregnancy and Lactation

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Brief Overview of Development

Tedizolid phosphate, the free acid form of tedizolid, is an oxazolidinone prodrug antibiotic that was licensed by Trius Therapeutics, Inc. for clinical development in all countries outside of Korea in 2007. Dong-A initiated the clinical development of tedizolid, the disodium salt of tedizolid phosphate, in Korea in 2006. Most in vivo non-clinical studies and early development studies including several Phase 1 clinical studies (TR701-101, TR701-102, and TR701-103) and a Phase 2 clinical study (TR701-104) used the tedizolid disodium salt in a solid tablet formulation. A free acid prodrug, tedizolid phosphate, was later formulated as an immediate release tablet for oral administration and a sterile lyophilized powder for injection and these formulations were used in most of the clinical development program, including both pivotal Phase 3 studies and an additional Phase 2 safety study (TR701-112 and TR701-113 and TR701-126 respectively). Oral tedizolid phosphate was found to be superior to the disodium salt with high bioavailability (TR701-107) and was selected as the drug product for commercialization. Tedizolid phosphate is the intended commercial drug product for both oral and IV administration in the targeted clinical indication. An oral suspension was also developed for paediatric studies in participants <12 years of age, and exposure tables reflecting oral administration include participants dosed with oral suspension as well as tablet. In September 2013, Cubist Pharmaceuticals Inc. acquired Trius Therapeutics and in January 2014, Cubist Pharmaceuticals LLC became the sponsor of the marketing application for the EU. On January 21, 2015, Cubist Pharmaceuticals LLC (at that time called Cubist Pharmaceuticals, Inc., and referred to hereafter as Cubist) was acquired by Merck & Co., Inc., Kenilworth, NJ, USA (known as MSD outside the United States and Canada). In January 2016, the marketing authorization holder (MAH) was transferred from Cubist to MSD. In August 2018, the MAH was further transferred to Merck Sharp & Dohme B.V. in the Netherlands (referred to hereafter as MSD). As of May 1, 2015, the MSD Safety Database became the official global safety database for tedizolid phosphate.

Tedizolid phosphate is indicated for both oral and intravenous (IV) administration in the treatment of acute bacterial skin and skin structure infections (ABSSSI), also known as complicated skin and soft tissue infections (cSSTI). Tedizolid phosphate was evaluated in a Phase 3 clinical study (MK-1986-002: A Phase 3 Randomized Double-blind Study Comparing TR-701 FA and Linezolid in Ventilated Gram-positive Nosocomial Pneumonia) for use in nosocomial pneumonia (NP), comprising hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). However, this study did not support the proposal of a new indication for HABP/VABP.

The initial development program was focused on the treatment of ABSSSI in adults (≥18 years of age), including elderly patients, and other indications in which gram-positive pathogens are major contributors to infection (e.g. SSTI-associated bacteremia).

In accordance with the approved paediatric investigation plan for ABSSSI, 5 paediatric studies have been completed in the paediatric population. These include three paediatric phase 1 PK and safety studies in adolescent patients (12 to <18 years), in patients 2 to <12

years, and in patients from birth to <2 years. Additionally, two phase 3 studies in patients with ABSSSI were completed: MK-1986-012: Phase 3 Study of IV to Oral 6-Day Tedizolid Phosphate Compared with 10-Day Comparator in Subjects 12 to <18 Years with cSSTI, and MK-1986-018, A Phase 3 Randomized, Active-comparator-controlled Clinical Trial to Study the Safety and Efficacy of MK-1986 (Tedizolid Phosphate) and Comparator in Subjects from Birth to less than 12 Years of Age with Acute Bacterial Skin and Skin Structure Infections (ABSSSI).

Phase 1 PK bridging studies were completed in Japan, China, and Korea by licensing partners Bayer and Dong-A in support of registration programs for the ABSSSI indication in their territories. Two completed Phase 3 clinical trials (Bayer protocols 16121 and 16099) were conducted by Bayer to support registration in China and Japan, respectively. Results from study 16099, completed in 2017, have been added to the clinical trial experience summarized in the Section SIII.2. Study 16099 was a randomized, open-label, active-controlled study in Japan, which included 83 adult patients treated with tedizolid 200 mg administered IV and/or oral once daily for 7-21 days for skin and soft tissue infections and SSTI- related bacteremia.

The following tables provide an overview of the patient exposure in the clinical development program for ABSSSI with a summary table showing total exposure. Duration of exposure is summarised for each category by counting patients who have received tedizolid phosphate for at least that number of days (ie, the number in the row for 1 day is the number of patients who have received 1 day or more). In tables summarising the duration of exposure for IV versus oral administration, patients who received 1 or more administrations of IV tedizolid phosphate and who also received oral tedizolid phosphate are counted once for each formulation. In these tables, person time is defined as the total number of years of tedizolid phosphate exposure for all patients in the referenced study group.

Clinical Trial Exposure by Duration

Table SIII.1: Extent of Exposure to Tedizolid Phosphate by Duration for IV and Oral Routes All Phase 1 to 3 Studies Safety Analysis Set

Duration of Exposure	Persons	Person Time (years)
1 day	306	0.8379
2 days	163	0.8928
3 days	62	0.5093
4 days	18	0.1971
5 days	77	1.0542
6 days	912	14.9821
≥ 7 days	735	20.6584
Any duration	2255	39.0332

Each person is counted once on each applicable duration category row.

Table SIII.2: Extent of Exposure to Tedizolid Phosphate by Duration for IV and Oral Routes All Phase 2 and 3 Studies Safety Analysis Set

Duration of Exposure	Persons	Person Time (years)
0-1 day	27	0.0712
2 days	23	0.1259
3 days	24	0.1971
4 days	17	0.1862
5 days	56	0.7666
6 days	908	14.9162
≥ 7 days	536	13.9333
Any duration	1,591	30.1966

Each person is counted once on each applicable duration category row.

Source: [MK1986-RMP: adam-adexsum]

Table SIII.3: Extent of Exposure to Tedizolid Phosphate by Duration for IV Administration All Phase 2 and 3 Studies Safety Analysis Set

Duration of Exposure	Persons	Person Time (years)
0-1 day	13	0.0329
2 days	12	0.0657
3 days	9	0.0739
4 days	11	0.1205
5 days	16	0.2190
6 days	409	6.7189
≥ 7 days	382	10.8750
Any duration of IV administration	852	18.1059

Each person is counted once on each applicable duration category row.
Table includes subjects who received 1 or more administrations of IV tedizolid phosphate.

Source: [MK1986-RMP: adam-adexsum]

Table SIII.4: Extent of Exposure to Tedizolid Phosphate by Duration for Oral Administration All Phase 2 and 3 Studies Safety Analysis Set

Duration of Exposure	Persons	Person Time (years)
0-1 day	14	0.0383
2 days	11	0.0602
3 days	19	0.1561
4 days	11	0.1205
5 days	52	0.7119
6 days	808	13.2735
≥ 7 days	467	12.0031
Any duration of oral administration	1,382	26.3635

Each person is counted once on each applicable duration category row.
Table includes subjects who received 1 or more administrations of oral tedizolid phosphate.

Source: [MK1986-RMP: adam-adexsum]

Clinical Trial Exposure by Dose

Table SIII.5: Extent of Exposure to Tedizolid Phosphate by Dose for IV Administration All Phase 2 and 3 Studies Safety Analysis Set

Dose of Exposure	Persons	Mean Duration (days)	Person Time (years)
Any dose	852	7.8	18.1059
Tedizolid Phosphate (200 mg)	797	7.8	16.9751
Tedizolid Phosphate (>200 mg)	0	0.0	0.0000
Tedizolid Phosphate (<200 mg)[a]	55	7.5	1.1308

Each person is counted once on each applicable dose category row.
Table includes subjects who received 1 or more administrations of IV tedizolid phosphate.
[a]Paediatric participants receiving weight-based dosing

Source: [MK1986-RMP: adam-adexsum]

Table SIII.6: Extent of Exposure to Tedizolid Phosphate by Dose for Oral Administration All Phase 2 and 3 Studies Safety Analysis Set

Dose of Exposure	Persons	Mean Duration (days)	Person Time (years)
Any dose	1,382	7.0	26.3635
Tedizolid Phosphate (200 mg)	1,317	6.9	24.9151
Tedizolid Phosphate (>200 mg)	0	0.0	0.0000
Tedizolid Phosphate (<200 mg)[a]	65	8.1	1.4484

Each person is counted once on each applicable dose category row.
Table includes subjects who received 1 or more oral tedizolid phosphate.
[a]Paediatric participants receiving weight-based dosing

Source: [MK1986-RMP: adam-adexsum]

Clinical Trial Exposure by Age and Gender

Table SIII.7: Extent of Exposure to Tedizolid Phosphate by Age Category and Gender for IV and Oral Routes All Phase 2 and 3 Studies Safety Analysis Set

Age Category (years)	Persons			Mean Duration (days)			Person Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Children (<12 years)	40	35	75	7.6	8.0	7.8	0.8269	0.7666	1.5935
Adolescents (12-17 years)	59	33	92	6.0	5.8	5.9	0.9637	0.5202	1.4840
Adults (18 - 64 years)	841	413	1,254	6.9	6.6	6.8	15.8115	7.4937	23.3052
Elderly (≥ 65 years)	95	75	170	8.4	7.9	8.2	2.1876	1.6263	3.8139
Total	1,035	556	1,591	7.0	6.8	6.9	19.7897	10.4069	30.1966

Source: [MK1986-RMP: adam-adexsum]

Table SIII.8: Extent of Exposure to Tedizolid Phosphate by Age Category and Gender for IV Administration All Phase 2 and 3 Studies Safety Analysis Set

Age Category (years)	Persons			Mean Duration (days)			Person Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Children (<12 years)	35	25	60	7.3	7.8	7.5	0.6982	0.5339	1.2321
Adolescents (12-17 years)	56	31	87	6.0	5.7	5.9	0.9254	0.4874	1.4128
Adults (18 - 64 years)	405	168	573	7.8	7.8	7.8	8.6984	3.5757	12.2741
Elderly (≥ 65 years)	76	56	132	9.0	8.6	8.8	1.8755	1.3115	3.1869
Total	572	280	852	7.8	7.7	7.8	12.1975	5.9084	18.1059

Table includes subjects who received 1 or more administrations of IV tedizolid phosphate.

Source: [MK1986-RMP: adam-adexsum]

Table SIII.9: Extent of Exposure to Tedizolid Phosphate by Age Category and Gender for Oral Administration All Phase 2 and 3 Studies Safety Analysis Set

Age Category (years)	Persons			Mean Duration (days)			Person Time (years)		
	Male	Female	Total	Male	Female	Total	Male	Female	Total
Children (<12 years)	37	33	70	7.9	8.2	8.1	0.8050	0.7447	1.5497
Adolescents (12-17 years)	30	15	45	5.9	6.0	6.0	0.4874	0.2464	0.7338
Adults (18 - 64 years)	752	386	1,138	6.9	6.7	6.8	14.1825	7.0310	21.2134
Elderly (≥ 65 years)	73	56	129	8.3	7.9	8.1	1.6564	1.2102	2.8666
Total	892	490	1,382	7.0	6.9	7.0	17.1312	9.2323	26.3635

Table includes subjects who received 1 or more oral tedizolid phosphate.

Source: [MK1986-RMP: adam-adexsum]

Clinical Trial Exposure by Race

Table SIII.10: Extent of Exposure to Tedizolid Phosphate by Race for IV and Oral Routes All Phase 2 and 3 Studies Safety Analysis Set

Race	Persons	Person Time (years)
Asian	279	7.5786
Black Or African American	179	2.9405
Multiple	8	0.2245
Not Reported	2	0.0602
Others	29	0.4764
White	1,094	18.9163
Total	1,591	30.1966

Source: [MK1986-RMP: adam-adexsum]

Clinical Trial Exposure by Special Populations

Table SIII.11: Extent of Exposure to Tedizolid Phosphate by Special Population for IV and Oral Routes
All Phase 2 and 3 Studies
Safety Analysis Set

Population	Persons	Person Time (years)
Pregnant women	2	0.0219
Lactating women	0	0.0000
Renal impairment (normal/mild, estimated creatinine clearance ≥ 60 mL/min at Baseline)	425	10.5109
Renal impairment (moderate/severe, estimated creatinine clearance < 60 mL/min at Baseline)	37	1.0322
Hepatic Disease (ALT or AST > 2x ULN at Baseline or positive for Hepatitis C antibodies)	364	6.6696
Hepatic impairment (moderate to severe, Child-Pugh Class B or C, Score ≥ 7, ALT or AST > 3x ULN at Baseline, ALT or AST = 3x ULN at Baseline and Total BIL ≥ 2x ULN at Baseline)	43	0.7913
Immuno-compromised (AIDS/HIV, neutropenia, transplant recipients)	0	0.0000

Each person is counted for each applicable population.
ULN = Upper Limit of Normal.

Source: [MK1986-ISS: adam-adexsum]

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Severe renal impairment: Defined as creatinine clearance (CrCl) <30 mL/min estimated by the Cockcroft-Gault formula OR requirement for peritoneal dialysis, plasmapheresis, haemodialysis, venovenous dialysis, or other forms of renal filtration	Pharmacokinetic parameters in severe renal impairment were not known at the time the protocol was prepared.	No	No dosage adjustments for tedizolid phosphate are required for patients with severe renal impairment or patients on hemodialysis
Severe hepatic impairment (defined as ALT or AST ≥8× upper limit of normal OR severe hepatic disease with Child Pugh score >9)	Pharmacokinetic parameters in severe hepatic impairment were not known at the time the protocol was prepared.	No	No dose adjustment is necessary for patients with hepatic impairment.
Complicated/deep ABSSSI: Infections associated with, or in close proximity to, a prosthetic device	Prosthetic device infections typically require prolonged treatment (>6 days)	Yes	The product has not been studied in this indication which may require a longer treatment course than currently recommended
Severe sepsis or septic shock Known bacteraemia at time of screening	Invasive infections require prolonged treatment (>6 days)	Yes	The product has not been studied in this indication which may require a longer treatment course than currently recommended.
Polymicrobial or deep seated infections requiring prolonged or combination therapy or adjunctive surgical interventions.	Consistent with regulatory guidance. Increased likelihood of gram-negative infection requiring broad spectrum therapy and/or additional surgical interventions confounding the assessment of efficacy in the clinical trial.	Yes	Sivextro is primarily active against Gram-positive bacteria. Tedizolid is not expected to adversely affect the potency of other concomitant antimicrobial agents. Product labeling addresses the need to consider gram-negative antimicrobial therapy when appropriate.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
Severe Immunocompromised states: Recent history of opportunistic infections where the underlying cause of these infections is still active (eg, leukaemia, transplant, acquired immunodeficiency syndrome [AIDS]) Receiving chronic systemic immunosuppressive therapy such as prednisone doses ≥20 mg per day for ≥3 of the last 12 months OR therapies that in the Investigator's judgment could predispose to opportunistic infections Last known CD4 count <200 cells/mm^3 in patients with AIDS Current or anticipated neutropenia with absolute neutrophil count (ANC) <1000 cells/mm^3	Immunocompromised states confound the assessment of efficacy. Patients with any history of severe immunosuppression were excluded in Phase 3 trials until efficacy and safety were established in the general population.	Yes	Patients with immunocompromising conditions or immunosuppressive therapies are normally monitored for lack of efficacy of any antimicrobial therapy as part of routine medical practice. Prescribing information states that controlled clinical trials did not include patients with neutropenia (neutrophil counts <1000 cells/mm^3) or severely immunocompromised patients
Potential interactions with linezolid: Triptan treatment for migraine headaches within 3 years In patients with uncontrolled hypertension, pheochromocytoma, carcinoid syndrome, or thyrotoxicosis, the use of the following medications within 2 days before the first infusion of study drug or planned use through the EOT Visit: Systemic directly and indirectly acting sympathomimetic agents (e.g. pseudoephedrine, phenylpropanolamine), vasopressive agents (e.g. epinephrine, norepinephrine), or dopaminergic agents (e.g. dopamine, dobutamine). Use of a small amount of a vasoconstrictor (e.g. lidocaine containing epinephrine)	These exclusion criteria are contraindications to use of linezolid, and were based on potential for serious adverse reactions due to MAO_A inhibition. Linezolid was the active control in the double blinded pivotal studies.	No	The potential for interactions due to MAO inhibition with tedizolid is considered to be very low. Tedizolid is a reversible inhibitor of MAO *in vitro;* however, no interaction is anticipated when comparing the IC50 and the anticipated plasma exposures in man. No evidence of MAO_A inhibition was observed in Phase 1 studies specifically designed to investigate the potential for this interaction.

Table SIV.1.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Exclusion Criterion	Reason for Exclusion	Is it Considered to be Missing Information?	Rationale (if not Included as Missing Information)
during a minor surgical procedure under local anaesthesia (e.g. incision and drainage) is allowed Use of the following medications within 14 days before the first infusion of study drug or planned use through the EOT Visit: • Monoamine oxidase A and B (MAOA and MAOB) inhibitors (e.g. phenelzine, isocarboxazid) • 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			
High tyramine diet	Linezolid has a current SmPC precaution advising patients to avoid large quantities of foods or beverages with high tyramine content while taking this medication. Quantities of tyramine consumed should be less than 100 mg per meal. Linezolid was the active control in the double blinded pivotal studies.	No	Clinical studies at the intended therapeutic dose of 200 mg of tedizolid phosphate demonstrated no clinically relevant increase in dietary tyramine sensitivity compared to placebo
Women who are pregnant or nursing, or who are of childbearing potential and unwilling to use an acceptable method of birth control (eg, intrauterine device, double-barrier method [eg, condoms, diaphragm, or cervical cap with spermicidal foam, cream or gel], or male partner sterilization (excluding women ≥2 years postmenopausal or surgically sterile)	No data on maternal or foetal safety were available at the time the pivotal studies were conducted.	No	No clinical studies are planned to further characterize risk in pregnant or lactating women. Current, prescribing information contains advice to prescribers based on non-clinical studies.

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program

Elderly

Use in different age ranges: Elderly patients were included in Phase 1 and Phase 3 studies of tedizolid phosphate. Study TR701-109 evaluated the PK, safety, and tolerability following a single oral administration of 200 mg tedizolid phosphate in healthy subjects ≥65 years of age (N=14 elderly and N=14 adult controls between 18 and 64 years of age). Table 1, Table 2, and Table 3 [Ref. 1.8.2: riskmgtsystem-combined: Annex 7] summarise the safety results for 170 elderly patients who received TR-701 or TR-701 FA in Phase 2/3 studies. Overall, in controlled Phase 3 studies, tedizolid exposure in subjects age ≥65 years old was 161 subjects and exposure in age ≥75 years old was 53 subjects. In the Phase 3 Controlled Studies group, the incidence of AEs was higher in the elderly age group (55.3%) than among younger patients (46.3%). Among those ≥65 years old, the incidence of AEs (55.3%) was not appreciably different from patients ≥75 years old (60.4%)). The rates of TRAEs in subjects ≥65 and ≥75 years old were similar to that of subjects 18 to 65 years old (19.3, 24.5 and 23.3%, respectively). No subject in any age group had a TRAE that was fatal or deemed an SAE. One subject >65 years old (0.7%) and 4 subjects 18 to 65 years old (0.5%) discontinued study drug due to a TRAE.

Overall the incidence of AEs in the controlled Phase 3 studies was similar in elderly patients when compared to the adult study population. SOCs of metabolism, investigations, musculoskeletal, skin and subcutaneous disorders, and vascular disorders/cardiac events were higher in the >65 year old age group. No increased incidence of nervous system disorders in general or in specific AEs, such as dizziness, was observed.

Need for laboratory screening prior to use: there is no anticipated need for special laboratory monitoring, ie, to measure hepatic or renal function prior to use of tedizolid phosphate, as the pharmacokinetics of tedizolid are not affected.

Effect of multiple co-existing impairments: There was no evidence of adverse effects of multiple pre-existing renal or hepatic impairments observed in clinical trial experience in elderly subjects.

Pregnant or Breast Feeding Women

Number of pregnancies and outcomes: There were a total of 4 patients in the clinical development program who had positive pregnancy tests (2 were treated with tedizolid phosphate and 2 were treated with linezolid). No pregnancy outcomes were reported for the 2

patients who received tedizolid phosphate despite multiple attempts to obtain follow-up information.

Implications for use under less controlled conditions: Appropriate methods to prevent pregnancy will be required for women with child-bearing potential enrolled in planned clinical trials. Screening tests for clinical trials will include serum pregnancy tests performed at local laboratories and confirmed at central laboratories.

In one case, the subject had a prior tubal ligation, therefore the screening test was not required under the protocol. It is unlikely that the study drug had any effect on the tubal ligation failure. The failure rate is low (2-3 pregnancies per 1,000 procedures; [Ref. 5.4: 04C0C9]).

The effects of tedizolid phosphate on a pregnancy or on a nursing child are not known, as there are no studies in pregnant women or mothers who breastfeed. Tedizolid was not teratogenic in mice or rats at exposure levels approximately 4-fold (in mice) and 6-fold (in rats) higher than the human exposure levels with 200 mg tedizolid phosphate daily. At higher exposure levels causing maternal toxicity in rats, related mild foetal toxicity was seen. No adverse effects were observed on growth, maturation, or measures of brain or reproductive function in the offspring of the pregnant animals exposed to tedizolid.

All cases of spontaneously reported exposure during pregnancy will be followed as part of routine surveillance, and the outcome of pregnancy will be periodically reported in safety update and benefit/risk reports.

Table SIV.3.1: Pregnancy Experience in Clinical Trials in Patients Treated with Tedizolid Phosphate

Age (Years)	Pregnancy Outcome	Comments
30	Unknown/ Lost to Follow-up	Patient had negative urine but positive serum pregnancy test result at the Screening Visit on 21 September 2010 and a second positive serum test result on 24 September 2010 (Day 4). The patient received tedizolid phosphate 200 mg orally once daily for 2 days and discontinued treatment. The outcome of the pregnancy is unknown. Numerous attempts were made to contact the patient, but she was lost to follow-up.
38	Unknown/ Lost to Follow-up	Patient had a history of tubal ligation, so a serum pregnancy test was not obtained at the Screening Visit due to the patient's surgical history. She agreed to use condoms and spermicide while participating in the study. The patient received tedizolid phosphate 200 mg IV once then 200 mg orally once daily from for five days. A positive serum pregnancy result was obtained from the End-of-Therapy Visit. The patient returned to the research site and the local lab results confirmed the positive result. Given the patient's last menstrual period date, the estimated date of conception was during study drug exposure, with an estimated date of delivery in August 2013. On Study Day 15, the patient was hospitalised for treatment of worsening kidney stones. Lithotripsy was performed and the patient was discharged home. The patient returned to the research site for her Post-Therapy Evaluation Visit. She reported having pain related to her kidney stones but had otherwise recovered. The patient was subsequently lost to follow-up despite multiple attempts at telephone contact and written correspondence. The outcome of the pregnancy is unknown.

Sources: ISS Listing 1.3.4, Clinical Study Report Narratives TR701-112 and TR701-113.

Patients With Hepatic Disease or Hepatic Impairment

Safety data for tedizolid phosphate in patients with hepatic impairment or hepatic disease were collected in both Phase 1 and Phase 2/3 studies. In an open-label study of a single oral dose of tedizolid phosphate 200 mg in subjects with severe or moderate hepatic impairment, defined by Child-Pugh scores of B-C, respectively, the $AUC_{0-\infty}$ were 22% and 34% higher, respectively, compared to matched healthy subject controls (n=8/group). Overall, tedizolid phosphate was well tolerated in patients with hepatic impairment or hepatic disease and most AEs were mild in severity. No clinically significant changes were noted in laboratory, vital sign, physical examination, or ECG data. C_{max} changed by less than 10% in subjects with moderate to severe hepatic impairment compared to controls. No dosage adjustment is necessary in subjects with moderate to severe hepatic impairment.

Patients with severe hepatic impairment were excluded from clinical trials, but patients with moderate hepatic impairment (Childs-Pugh class B-C, or a total score ≥7) or pre-existing hepatic disease (manifested by elevations of alanine aminotransferase or aspartate aminotransferase at study entry, or a baseline test positive for Hepatitis C antibodies) were enrolled in the Phase 2/3 studies. In the Phase 3 controlled studies, the incidence of TEAEs in the tedizolid phosphate group was comparable in patients with hepatic disease compared to those with normal hepatic function (48.3% vs 48.0%, respectively)
[Ref. 1.8.2: riskmgtsystem-combined: Annex 7] (Table 4). The number of TRAEs in patients with hepatic disease and patients with normal function were also similar (26.9% and 21.9%, respectively).

Patients With Renal Impairment

Safety data for tedizolid phosphate in patients with renal impairment were collected in both Phase 1 and Phase 2/3 studies. In an open-label study of single dose tedizolid phosphate 200 mg IV, subjects with advanced renal impairment (estimated glomerular filtration rate [eGFR]<30.0 mL/min/1.73 m^2, n=8), with or without haemodialysis were compared with matched control subjects with normal renal function (eGFR ≥80.0 mL/min/1.73 m^2, n=8). Results show that tedizolid was well tolerated in this population. Only 1 subject experienced a severe AE (nausea and vomiting) and no SAEs were reported during treatment. No clinically significant changes were noted in laboratory, vital sign, physical examination, or ECG data. Following administration of a single IV dose of tedizolid phosphate intravenously, the C_{max} and $AUC_{0-\infty}$ were changed by less than 10% compared to healthy subject controls with normal renal function. Haemodialysis did not result in meaningful removal of tedizolid from the systemic circulation. No dosage adjustment is necessary in patients with severe renal impairment or patients on haemodialysis.

Patients with severe (advanced) renal impairment (including dialysis patients) were excluded from Phase 2/3 clinical trials, but patients with less severe renal impairment (ie, estimated creatinine clearance <60 mL/min but not requiring dialysis) were enrolled. In the controlled Phase 3 studies, there were 57 patients with moderate to severe renal impairment identified at baseline (based on calculated creatinine clearance) in the combined safety population (comprised of 1025 patients with creatinine clearance results). In the controlled Phase 3 studies, among the tedizolid phosphate treatment group, 38 of 57 patients (66.7%) with renal

impairment experienced TEAEs compared with 451 of 968 (46.6%) in patients with no renal impairment ([Ref. 1.8.2: riskmgtsystem-combined: Annex 7] (Table 5)). Treatment related and serious TEAEs were reported for 11 and 8 patients, respectively, in the tedizolid phosphate subgroup with renal impairment. Overall, the safety profile of tedizolid phosphate was similar in patients with normal or mild renal impairment compared to patients with moderate to severe renal impairment.

Myelosuppression resulting in thrombocytopenia or anaemia has been reported in retrospective studies of patients with renal impairment who were treated with linezolid for gram positive infections [Ref. 5.4: 04C03H]. The frequency of anaemia (defined as haemoglobin <10 g/dL) was 71.4% in patients with end stage renal disease (ESRD) who received mean duration of 15±8.8 days of linezolid and was significantly higher than patients with non-end stage renal disease (36.5%, P=0.003). Thrombocytopenia (defined as platelet count<100,000 cells/mm^3) was also more common in patients with ESRD (78.6%) than in patients with non-end stage renal disease (42.9%, P=0.03). These hematologic abnormalities resulted in premature discontinuation of linezolid in approximately 40% of ESRD patients in this study.

In the original ISS (including all Phase 2/3 clinical trials except MK-1986 005 and MK-1986 006), the incidence of TEAEs in patients receiving tedizolid phosphate in the Blood and Lymphatic System Disorder System Organ Class was reviewed by renal function status based on baseline estimated creatinine clearance (ISS Table 1.4.5.7.1). There were no reported events of thrombocytopenia. The overall incidence of anaemia was low in both the tedizolid phosphate and linezolid safety analysis sets (ISS Table 1.4.3.1.1). There were 6 TEAEs of anaemia in 1050 patients (0.6%) in the tedizolid safety analysis set and 1 event of anaemia reported in 662 patients (0.2%) in the linezolid analysis set. One of the TEAEs of anaemia occurred in a patient with moderate/severe renal impairment. There was only 1 report of white blood cell count decreased in 1050 patients in the tedizolid safety analysis set (in a patient with normal or mild renal impairment), and no reports of leukopenia or neutropenia. None of the events were serious or led to discontinuation of study treatment.

Patients With Other Relevant Co-Morbidity

Cardiovascular co-morbidity: There is no evidence to support a risk of pro-arrhythmogenic effect of tedizolid based on the results of a thorough QT study, the results of *in vitro* studies in cells expressing the human ether-à-go-go-related gene, and ECG studies in telemeterised dogs. In a randomized, positive and placebo-controlled crossover thorough QTc study, single doses of 200 mg and a supratherapeutic dose of 1200 mg tedizolid phosphate showed no significant effects on QTc interval over a 24-hour period which included times corresponding to peak plasma concentrations. Tedizolid phosphate had no effects on heart rate, PR and QRS interval duration, or cardiac morphology.

Across the Phase 2 and Phase 3 studies, subjects with potential QT prolongation AEs and pre-existing cardiovascular disorders are presented in [Ref. 1.8.2: riskmgtsystem-combined: Annex 7] Table 6. There were no AEs identified by the search criteria, therefore there are no data to suggest cardiac safety concern associated with tedizolid.

In the original ISS Phase 2/3 studies (not including Bayer studies 16121 and 16099), 11 patients had potentially clinically significant abnormalities in QTcB, QTcF, or changes >60 msec relative to baseline. None of these findings were associated with cardiac AEs. Most of the patients had pre- existing cardiovascular conditions. Since the data are limited to assess the cardiac safety in patients with pre-existing cardiovascular conditions, this has been maintained in the list of safety concerns as "missing information".

In the Phase 3 study 16121 in China, Taiwan, the Philippines and the US, no clinically meaningful changes were noted between screening and day 7 in ventricular rate, PR duration, QRS duration, QT interval corrected according to Bazett or Fridericia or QT duration in both treatment groups in this study. Worst post-baseline and change from baseline distribution of QTcB and QTcF showed that 5 (1.8%) subjects in the tedizolid group had a post-baseline QTcB value >500 msec; while 1 subject in the tedizolid group had a post-baseline QTcF value >500 msec. None of these changes were considered treatment-related adverse effects. Review of the cases of interest did not reveal any indication of new identified or potential risk for QT prolongation associated with tedizolid. A review of the 2 patient cases where QTc was > 500 msec revealed that ECG changes may have been confounded by pre-existing conditions or medications. Review of the other cases with QTc changes >60 msec from baseline did not reveal any cardiac TEAEs to suggest sequelae for the ECG changes.

In the Phase 3 study 16099 in Japan, over 90% of subjects (N=83 tedizolid group) showed ≤ 30 msec increase in the QTcF and QTcB at the EOT, and there was no clinically relevant change overall. One subject (1.2%) in the tedizolid group had a baseline QTcB value >500 msec, while no subject had a baseline QTcF value >500 msec. None of these findings were considered clinically significant by the investigators; they seemed to be a physiological variation, or had related medical history to explain the observed QT values. Increases in QTcB >60 msec at EOT were not observed; whereas, an increase in QTcF >60 msec was observed in only 1 subject. No clinically meaningful events were observed.

Immuncompromised patients: Severely immunocompromised patients including transplant patients, patients with severe immunosuppression due to HIV infection (AIDS), solid organ or hematopoietic stem cell transplants, chronic corticosteroid therapy, and patients with known or anticipated neutropenia (absolute neutrophil counts <1000 cells/mm^3) were excluded from clinical trials, as these conditions were to be studied once efficacy and safety was established in the general population. There are no anticipated safety issues in patients with these forms of immunosuppression (eg, chronic corticosteroid use).

Diabetic patients: The data are limited for evaluation of the risk-benefit profile in diabetic patients with ABSSSI. Adverse event data by presence of a medical history of diabetes mellitus/hyperglycemia across the Phase 2 and Phase 3 studies are presented in [Ref. 1.8.2: riskmgtsystem-combined: Annex 7] Table 7 and Table 8. In the original Phase 3 studies, only 58 (8%) of patients in the tedizolid group were diabetic, and another 30 patients were studied in the uncontrolled Phase 2 trials; 25 subjects were enrolled and treated with tedizolid in a post-approval efficacy study (16121), and 30 diabetic patients were randomized to tedizolid in the Japan post-approval efficacy study (16099). Differences between the response rates seen in the diabetic patient subgroup in protocol 16121 were similar to those noted in study TR701-112 and TR701-113 [Ref. 5.3.5.3: integrated-summary-of-efficacy:

Table 16.2], [Ref. 5.3.5.3: integrated-summary-of-efficacy: Table 39.4] and [Ref. 5.3.5.3: integrated-summary-of-efficacy: Table 39.8] and [Ref. 5.3.5.1: p006mk1986: Table 9-22]. There were no differences in response rates in the diabetic subgroup for the primary efficacy endpoint in the 16099 study. The clinical response rate in patients with medical history of diabetes mellitus/hyperglycemia in this study was similar to non-diabetic patients as determined at TOC in the Microbiologically Evaluable (ME-MRSA) subset: 9 of 11 responders (81.8%) vs. 16/18 responders in non diabetic patients (88.6%) [Ref. 5.3.5.1: p005: Table 9-29].

Interpretation of treatment differences in small patient subgroups is hindered by variations in disease characteristics or concomitant conditions that impact treatment outcomes, and which are not fully controlled by randomization. The tedizolid diabetic subgroup in study 16121 comprised of 26 subjects in the intent to treat (ITT) analysis set (demographics 26 Asian with 22 patients from China and 4 Asian patients from other countries); there were no patients with diabetic foot infections enrolled (this was an exclusion criterion for this study). Fifty-nine (59) subjects were included in the modified ITT analysis (all treated subjects) for the primary endpoint (decrease in lesion size at the 48-72 hour visit). Of these, 25 subjects were treated in the tedizolid group, 22 had cellulitis/erysipelas, 3 had major abscesses, and none of the patients had wound infections. None of the tedizolid subset received adjunctive therapy; 2 subjects in the linezolid group received aztreonam, and one subject received both aztreonam and metronidazole. Surgical drainage was performed for all major abscesses. In the tedizolid mITT subset of diabetic patients, 16/25 subjects (64%) did have reduction $\geq$ 20% in lesion size at 48-72 hours, and in the clinically evaluable subset, 14/19 subjects (73.7%) were assessed by the investigators as clinical cures at the post therapy evaluation visit. All patients with major abscesses who were treated with tedizolid (mITT subset) were considered responders at the 48-72 hours and cure at post therapy evaluation (PTE). There was no experience with wound infection in the tedizolid group of diabetic patients. Of the 9 tedizolid subjects who were deemed nonresponders, 2 were indeterminate at the early and late endpoints. Of the total patients enrolled in study 16121 who received tedizolid phosphate, 51 provided PK samples, which facilitated estimation of tedizolid PK exposure parameters. Of the 51 patients with PK information, only 5 were diabetic. The distribution of tedizolid PK exposure in the 5 diabetic patients was comparable to that in the non- diabetic patients. This is consistent with the comparable distributions of PK exposure in diabetic and non-diabetic patients in the global Phase 3 studies. Based on an exposure-response modeling analysis using the PK data from the 51 study 16121 patients, no statistically significant correlation between tedizolid exposure and the early clinical response endpoint was identified.

Importantly, population PK analysis from studies TR701-112 and TR701-113 also showed no difference in tedizolid systemic exposure in diabetic versus non-diabetic patients. Underlying conditions such as diabetic peripheral neuropathy and retinopathy may confound the assessment of drug safety in patients with diabetes. These observations together suggest that the lower response in diabetic patients could not be attributed to tedizolid plasma exposure, though PK data are limited in this population.

Patients With a Disease Severity Different From the Inclusion Criteria in the Clinical Trial Population

Patients with severe sepsis were excluded from the pivotal studies, as the standard of care is to treat these serious infections until clinical stability is achieved with negative blood cultures, for at least 10 to 14 days and up to 4 weeks. Tedizolid is expected to be effective in the treatment of gram-positive infections, including bacteraemic ABSSSI, as tedizolid is widely distributed in the blood, intracellular fluid, and tissues, with bactericidal activity against gram-positive pathogens. All bacteraemic patients with ABSSSI treated with tedizolid phosphate in clinical trials had the pathogen eradicated from the blood stream with 6 days of therapy.

Sub-Populations Carrying Known and Relevant Polymorphisms

Not applicable.

Patients of Different Racial and/or Ethnic Origin

Tedizolid does not appear to undergo significant oxidative metabolism, therefore it is unlikely to be affected by ethnic or racial factors. There was no large difference in plasma concentration profiles of tedizolid between Japanese (n=60) and US subjects in PK studies. There was also no clinically significant difference in the PK parameters and safety profile among different ethnic groups and races in population PK analysis in a Phase 2 study (TR701-104, cSSTI patients), which included 140 white patients, 45 black patients, 1 Asian patient, and 1 patient of another race.

Adverse event data by Race in the Phase 2 and 3 clinical trials are presented in [Ref. 1.8.2: riskmgtsystem-combined: Annex 7] Table 9.

The incidence of treatment emergent AEs was not substantially different between racial subgroups and between treatments in the Phase 3 Bayer 16121 and 16099 clinical trials when comparing results from tedizolid phosphate to linezolid (Table ISS 87). Overall, in the controlled Phase 3 trials, the incidence of AEs in tedizolid-treated subjects was higher in the Asian (54.2%) population compared to white (47.7%) or black/African American (31.6%) populations; however, the rate of TRAEs was similar in Asian (22.2%) and white (24%) populations.

China International Multicenter Trial (Bayer Study 16121)

Bayer AG conducted a Phase 3 randomized, double-blind, multicenter study (protocol 119-2631/16121) comparing the efficacy and safety of intravenous to oral 6-day tedizolid phosphate to intravenous to oral 10-day linezolid for the treatment of acute bacterial skin and skin structure infections, at 52 study centers in China, the Philippines, Taiwan and the US. This trial enrolled a total of 598 subjects randomized to the study medication, 589 subjects (98.5%) were treated, 292 (97.3%) subjects with tedizolid and 297 (99.7%) subjects with linezolid. Overall, a total of 517 (86.5%) subjects completed the study treatment and 81 (13.5%) subjects prematurely discontinued the study treatment. The number of subjects who completed study treatment (tedizolid: 261 [87.0%] subjects; linezolid: 256 [85.9%]

subjects) and the primary reasons reported for subjects who discontinued study treatment were balanced between the tedizolid group and linezolid group.

Of the 300 subjects assigned to tedizolid treatment, 69.7% were male. The mean age was 45.7 years (range 18 to 85 years). Similarly, in the linezolid group, 64.4% of subjects were male. The mean age was 47.5 years (range 18 to 85 years). Over 60% of the subjects were Asian (tedizolid: 63.7%; linezolid: 64.8%), and over 30% were White (tedizolid: 33.7%; linezolid: 31.2%).

Early clinical response (based on lesion size reduction) at 48-72 hours after the first infusion of study drug, which was the primary efficacy variable, was observed in 75.3% of subjects treated with tedizolid and 79.9% of subjects treated with linezolid in ITT analysis set. Treatment difference between the 2 treatment groups was -4.6% with 95% CI: -11.2, 2.2.

The lower limit of the 95% CI for treatment difference was below -10%, which was the pre-defined margin for the non-inferiority, therefore non- inferiority of tedizolid to linezolid was not achieved for the early clinical response in the ITT analysis set. Non-inferiority was demonstrated for the secondary efficacy variables which included programmatic determination of clinical response at the EOT visit and at the Post Treatment Evaluation (PTE). Programmatic determination of clinical response (clinical success) at the End of Treatment (EOT) visit, was observed in 82.0% of subjects in the tedizolid group and 84.2% subjects in the linezolid group (treatment difference: -2.2%; 95% CI: -8.3, 3.8) in the ITT analysis set. The investigator's assessment of clinical success at PTE (Test of Cure visit) was observed in 79.7% of the subjects in the tedizolid group and 81.9% of the subjects in the linezolid group in ITT analysis set, and the treatment difference was -2.2% (95% CI: -8.6, 4.1).

The safety analysis set included 380 Asian subjects (187 subjects in the tedizolid group and 193 subjects in the linezolid group) and 209 non-Asian subjects (105 subjects in the tedizolid group and 104 subjects in the linezolid group) who were included in the ITT analysis set and received at least 1 dose of active drug during the study. The overall incidence of TEAEs in the tedizolid group was comparable with the linezolid group (tedizolid: 49.7% of subjects; linezolid: 45.8% of subjects). Most TEAEs were mild or moderate in intensity and severe TEAEs were only reported in 12 subjects with tedizolid and 7 subjects with linezolid. The most commonly reported TEAE by PT (occurred in $\geq$ 5% subjects in either treatment group) was nausea (tedizolid: 15 [5.1%] subjects; linezolid: 14 [4.7%] subjects). Study drug-related TEAEs by investigator assessment were reported in 61 (20.9%) subjects in the tedizolid group and 47 (15.8%) subjects in the linezolid group, respectively. Of those events, phlebitis was reported more frequently in the tedizolid group (tedizolid: 8 [2.7%] subjects and linezolid: 0 subjects); all events were non-serious infusion site reactions. Infusion site reactions (phlebitis) were reported more frequently among Asian patients at 4 study centers in China. These findings suggest a higher frequency of infusion-related reactions (phlebitis) than was observed in previous clinical studies with tedizolid phosphate. No deaths were reported in this study. SAEs were reported in 11 (3.8%) subjects in the tedizolid group and 8 (2.7%) subjects in the linezolid group. There was no study-drug related serious TEAE in the study. In general, tedizolid was shown to be well tolerated.

ABSSSI in Japanese Patients- (Bayer Study 16099)

Bayer AG conducted a Phase 3 randomized, multicenter, prospective, open-label, active-controlled study, protocol 16099, that evaluated the efficacy and safety of tedizolid phosphate in Japanese adult patients with SSTI and SSTI-related bacteremia. Tedizolid was administered 200 mg IV for at least 3 days with the option to switch to oral tablets once daily for 7 to 14 days for patients with SSTI or 200 mg IV for 7 to 21 days for SSTI-related bacteremia. Linezolid was included as a reference arm (patients were to receive linezolid 600 mg twice daily by IV for at least 3 days with the option to switch to oral administration twice daily for 7 to 14 days for SSTI or IV for 7 to 21 days for SSTI-related bacteremia). The study was conducted at 46 study centers in Japan. Overall, 83 patients were treated with tedizolid 200 mg once daily and 41 patients were treated with 600 mg linezolid twice daily. Overall, a total of 110 (88.7%) subjects completed the study treatment and 14 (11.3%) subjects prematurely discontinued the study treatment. The number of subjects who completed study treatment (for tedizolid: 72 (86.7%) subjects; linezolid: 38 (92.7%) subjects) and the primary reasons reported for subjects who discontinued study treatment were balanced between the tedizolid group and linezolid group.

Of the 83 subjects assigned to tedizolid treatment, 65.1% were male. The mean age was 63.2 years (range 25 to 94 years). Similarly, in the linezolid group, 68.3% of subjects were male. The mean age was 63.3 years (range 25 to 91 years). All subjects were Asian and of Japanese ethnic origin.

The clinical cure rates at the TOC were 92.6% (25/27 subjects) in the tedizolid group and 88.9% (8/9 subjects) in the linezolid group for the SSTI subjects of the microbiological evaluable population with MRSA (ME-MRSA). The lower limit of the 95% CI was 75.7% in the tedizolid group, above the pre-defined efficacy threshold of 30%. No subject in the tedizolid group and 2 subjects in the linezolid group had bacteremia in the ME-MRSA population. At TOC in the linezolid group, 2 subjects (100%) showed indeterminate as the clinical response and eradication as the microbiological response. In the SSTI subjects of ME-MRSA, the effective rates at the EOT were 93.1% (27/29 subjects) in the tedizolid group and 90.0% (9/10 subjects) in the linezolid group.

The safety analysis set included 124 patients. The incidence rate of TEAEs was 79.5% (66/83 subjects) in the tedizolid group and 75.6% (31/41 subjects) in the linezolid group. Study-drug related TEAEs were reported by 25/83 subjects (30.1%) in the tedizolid group and 16/41 subjects (39.0%) in the linezolid group. The most commonly (≥ 5%) reported TEAEs in the tedizolid group were nausea, injection site pain, alanine aminotransferase increased, and dermatitis contact (each 6.0%, 5/83 subjects). The most frequently reported TEAEs in the linezolid group were dermatitis contact (14.6%, 6/41 subjects), constipation, diarrhoea, nausea, vomiting, and injection site pain (each 9.8%, 4/41 subjects), and hepatic function abnormal and cellulitis (each 7.3%, 3/41 subjects). For any TEAE recorded, the difference in the incidence rates between the two treatment groups was less than 10%. One death was reported in the linezolid group, whereas there were no deaths in the tedizolid group. In this study, a treatment-emergent SAE was reported in 7 subjects (8.4%) in the tedizolid group and 4 subjects (9.8%) in the linezolid group. The most commonly reported preferred term (reported for ≥ 2% of the total subjects) in which subjects had any treatment-

emergent serious AE was cellulitis (1.2% in the tedizolid group and 4.9% in the linezolid group). A drug-related SAE by investigator assessment was observed in only one subject in the linezolid group (bone marrow failure). Adverse events of special interest were observed in 11 subjects (2.4% [2/83 subjects] in the tedizolid group and 22.0% [9/41 subjects] in the linezolid group). All adverse events of special interest were for the safety concern of myelosuppression, and included the AE preferred terms of anemia, thrombocytopenia and leukopenia/neutropenia.

Three of 83 subjects (3.6%) in the tedizolid group and 1/41 subject (2.4%) in the linezolid group prematurely discontinued the study treatment because of TEAEs. These events were not drug-related. The SOC of all TEAEs resulting in discontinuation of study drug was Infections and Infestations. In general, tedizolid was shown to be well tolerated and no new safety signals were detected in this study.

There were geographic differences in the reported rates of TEAEs, but this is consistent with regional medical care practices and is unlikely to reflect any ethnic or racial differences in the safety profile, as the magnitude of difference was consistent between the treatment groups in the controlled trials [Ref. 1.8.2: riskmgtsystem-combined: Annex 7], Table 10.

SIV.4 Conclusions on the Populations not Studied and Other Limitations of the Clinical Trial Development Program

Table SIV.4.1: Safety Concerns due to Limitations of the Clinical Trial Program

Missing Information		Outstanding Concern?
Safety concern	**Comment**	**Yes/No**
Serotonin syndrome (in patients receiving drugs with serotonergic potential)	No clinical studies have been conducted with co-administration of tedizolid phosphate and monoamine oxidase inhibitors (MAOI), or serotonergic agents such as selective serotonin reuptake inhibitors (SSRIs) serotonin- norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, 5-HT1 (serotonin) receptor agonists (triptans), meperidine, buspirone, tramadol, and dextromethorphan because these drugs were contraindicated for the active comparator drug linezolid. No interaction is anticipated based on a high therapeutic index for MAO inhibition when comparing IC_{50} and the anticipated tedizolid plasma exposures (C_{max}) in man. Tedizolid phosphate at doses up to 30-fold above the human equivalent did not increase the serotonergic response in 5-HTP mouse head twitch model.	No
Pregnancy and breastfeeding women	Women who were pregnant or nursing, or who were of childbearing potential and unwilling to use an acceptable method of birth control were excluded from the clinical trials. There are no data from the use of tedizolid phosphate in pregnant women and it is unknown whether tedizolid or its metabolites are excreted in human milk. Embyro-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. The no observed adverse effect levels (NOAELs) for foetal toxicity in mice as well as maternal and foetal toxicity in rats 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 was found to be excreted in the breast milk of rats.	No

Table SIV.4.1: Safety Concerns due to Limitations of the Clinical Trial Program

Missing Information		Outstanding Concern?
Severely Immunocompromised patients (eg, patients with neutropenia, transplant recipients, HIV/AIDS)	No data from clinical trials.	Yes
Prolonged treatment >7 days	Patients with severe infections (eg, diabetic foot infections, decubitus or ischaemic lesions, severe burns or gangrene; requiring prolonged treatment of bacteraemia, bone, or joint infections complicating ABSSSI) were excluded from the clinical trials. Bayer study 16099, completed in 2017, was added to the clinical trial experience summarized in Section SIII.2. This was a randomized, open-label, active- controlled study in Japan, which included 83 adult patients treated with tedizolid 200 mg administered IV and/or oral once daily for 7-21 days for skin and soft tissue infections, including major abscess, chronic pyoderma, and wound infections and SSTI- related bacteremia. In Bayer study 16099, the mean number of total administrated days for 83 subjects treated with tedizolid was 10.3 ± 3.9 days in the tedizolid group ranging from 1 to 21 days of total therapy. Additionally, paediatric study P018, completed in 2023 and included in the clinical experience summarized in Section SIII.2, permitted tedizolid phosphate therapy for 6 to 10 days, based on the investigator's clinical judgment. 47 participants received more than 6 days of therapy; the mean duration was 7.8 days.	No
Severe renal impairment	A pharmacokinetic study has indicated that no dose adjustment is required in severe renal impairment or in dialysis patients.	No
Severe hepatic impairment	A pharmacokinetic study has indicated that no dose adjustment is required in severe hepatic impairment.	No
Elderly patients	170 patients older than 65 years were enrolled in pivotal studies.	No
Diabetic patients	148 patients with diabetes mellitus and ABSSSI were enrolled and treated in 2 uncontrolled studies with tedizolid phosphate ≥200 mg administered orally for 5-7 days, in 4 Phase 3 controlled studies with tedizolid phosphate 200 mg administered orally or IV for 6 days (approximately 10% of the total study population).	Yes
Patients with polymicrobial (Gram positive and Gram negative) infections	Patients with polymicrobial infections were generally excluded from clinical studies (except for those with wound infection where appropriate adjunctive therapy was allowed); few patients in the pivotal adult ABSSSI studies (N=13)[1] and no patients in the adolescent ABSSSI study had mixed gram-positive/gram-negative infection.	Yes
High tyramine diet	The lack of in vivo findings from healthy volunteer studies with tedizolid phosphate following tyramine and pseudoephedrine challenge and the lack of signal in non-clinical studies suggests that the risk for clinically significant MAO inhibition is very low.	No
Emerging resistance	The possible presence of L3 and L4 ribosomal protein mutations or any other new mechanisms causing resistance to both linezolid and tedizolid was not identified in any clinical isolates in a 5-year surveillance study.	No
Drug-drug interactions via CYP3A4	The potential for induction of CYP3A4 leading to clinically significant drug-drug interactions was recently evaluated in clinical studies with midazolam and ruled out based on results.	No

Table SIV.4.1: Safety Concerns due to Limitations of the Clinical Trial Program

Missing Information		Outstanding Concern?
Drug-drug interactions via BCRP or OATP-1B1	The potential risk for interactions with substrates of the efflux transporter BCRP was assessed in a study with rosuvastatin alone or in combination with the oral administration of Sivextro film-coated tablets. Systemic interactions via OATP-1B1 inhibition are considered unlikely. The potential risk is adequately managed by product labeling.	No
Cardiac safety (QTc/Torsades de Pointes) in patients with pre-existing cardiac dysfunction	The potential for QT prolongation leading to serious ventricular arrhythmias in patients with pre-existing cardiovascular risk factors has not been fully evaluated in clinical studies. There were no significant new findings observed in Bayer studies 16121 and 16099.	No

[1] Reference: Clinical Study report TR701-112 (1986-009), Table 11-48 and TR701-113 (1986-010), Table 11-49.

Table SIV.4.2: Exposure of Special Populations Included or not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	There were only two pregnant patients exposed to tedizolid phosphate, and no breastfeeding women were exposed.
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	▪ There were 13 patients with hepatic impairment who were included in all controlled Phase 3 safety population. ▪ There were 57 patients with moderate to severe renal impairment in the combined Phase 3 safety population. ▪ There were no data for patients with cardiovascular impairment. ▪ There were no data for immunocompromised patients. ▪ There were no data for patients with a disease severity different from inclusion criteria in clinical trials.
Population with relevant different ethnic origin	No relevant PK or safety differences in the Asian population compared to other ethnic groups.
Subpopulations carrying relevant genetic polymorphisms	Not evaluated (none anticipated)

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

A summary of the worldwide distribution of tedizolid phosphate for the cumulative period from market introduction to 20-JUN-2025[1] is presented below based on the available data. This estimation was based on the assumption that patients received either 6 days IV or 6 days oral administration (i.e., there was no IV to oral switch). Estimates of exposure were based on the average days of therapy (DOT) from the Antimicrobial Resistance (AMR) database for US hospitals[2] from the second half of 2014 through the end of 2015. No other data are available for DOT in other countries where tedizolid phosphate is marketed. For tedizolid phosphate powder for injection, the average DOT was 6.1 days and for tedizolid phosphate tablets, the average DOT was 5.3 days. Patient exposure estimates were calculated from our Company's internal distribution data from the Worldwide Financial Reporting System (WFRS), and the Financial Sharing Area (FSA) database(s). Patient exposure estimates were calculated from expanded distribution categories to provide a more accurate estimate of patient exposure worldwide. The effects of this update may be apparent when comparing current estimates of patient exposure to those of prior reporting periods.

SV.1.2 Exposure

The estimated number of doses of tedizolid phosphate distributed worldwide from product launch through 20-JUN-2025 is 3,736,897. This corresponds to 622,817 estimated patient courses of treatment.

SV.2 Post-Authorization Use in Populations not Studied in Clinical Trials

No data are available describing post-authorization patient exposure in the special populations identified in RMP Module SIV as having no or limited exposure.

[1] This estimate of patient exposure from market introduction is based on the availability of monthly drug distribution figures; hence, this estimate has been calculated from market introduction to 31-MAY-2025, rather than from market introduction to 20-JUN-2025 (DLP).

[2] Source: AMR USA 2H 2014, 2015.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for Misuse for Illegal Purposes

Not applicable.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2 New Safety Concerns and Reclassification With a Submission of an Updated RMP

This section is not applicable as there are no safety concerns identified for tedizolid phosphate.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

There are no identified or potential risks for tedizolid phosphate.

SVII.3.2 Presentation of the Missing Information

There is no missing information for tedizolid phosphate.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table SVIII.1: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

The MAH maintains systems and standard practices for routine pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g. individual case safety reports, PSURs, etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labeling, and liaising with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Not Applicable.

III.2 Additional Pharmacovigilance Activities

Not Applicable.

III.3 Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

There are no ongoing or proposed post-authorization efficacy studies (PAES) for tedizolid phosphate.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1 Routine Risk Minimization Measures

Not Applicable.

V.2 Additional Risk Minimization Measures

Not Applicable.

V.2.1 Risk Minimization Measure Failure

Not Applicable.

V.2.2 Analysis of Risk Minimization Measure Failure

Not applicable.

V.2.3 Revised Proposal for Risk Minimization

Not applicable.

V.3 Summary of Risk Minimization Measures

Not Applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN BY PRODUCT

Summary of risk management plan for tedizolid phosphate

This is a summary of the risk management plan (RMP) for tedizolid phosphate. The RMP details important risks of tedizolid phosphate, how these risks can be minimised, and how more information will be obtained about tedizolid phosphate's risks and uncertainties (missing information).

The Summary of product characteristics (SmPC) for Sivextro and its package leaflet give essential information to healthcare professionals and patients on how tedizolid phosphate should be used.

I. The Medicine and What it is Used For

Sivextro 200 mg film-coated tablet is authorised for the treatment of acute bacterial skin and soft structure infections (ABSSSI) in adult patients and paediatric patients weighing at least 35 kg (see SmPC for the full indication). It contains tedizolid phosphate as the active substance and it is given by oral administration once daily for 6 days.

Sivextro 200 mg powder for concentration for solution for infusion is authorised for the treatment of acute bacterial skin and soft structure infections (ABSSSI) in adult and paediatric patients (see SmPC for the full indication). It is given either as a 200 mg dose once daily in adult patients and paediatric patients weighing at least 35 kg, or as weight-banded dosing twice daily in paediatric patients weighing less than 35 kg (see SmPC for dose bands). It contains tedizolid phosphate as the active substance and it is given by intravenous infusion over 60 minutes once or twice daily for 6 days.

Sivextro 20 mg/mL powder for oral suspension is authorised for the treatment of acute bacterial skin and soft structure infections (ABSSSI) in adult and paediatric patients (see SmPC for the full indication). It is given either as a 200 mg dose once daily in adult patients and paediatric patients weighing at least 35 kg, or as weight-banded dosing twice daily in paediatric patients weighing less than 35 kg (see SmPC for dose bands). It contains tedizolid phosphate as the active substance and it is given by oral administration once or twice daily for 6 days.

Further information about the evaluation of the benefits of Sivextro can be found in the EPAR for Sivextro, including in its plain-language summary, available on the EMA website, under the medicine's webpage [link to product's EPAR summary landing page on the EMA webpage https://www.ema.europa.eu/en/medicines/human/EPAR/sivextro]

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Sivextro, together with measures to minimise such risks and the proposed studies for learning more about the risks of Sivextro, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Sivextro is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of Sivextro are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient evidence of a link with the use of Sivextro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table II.A.1: List of Important Risks and Missing Information

List of Important Risks and Missing Information	
Important identified risks	• None
Important potential risks	• None
Missing information	• None

II.B Summary of Important Risks

There are no important identified or potential risks for Sivextro.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Sivextro.

II.C.2 Other Studies in Post-Authorisation Development Plan

All studies sponsored by the MAH have been completed.

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ANNEXES

ANNEX 4 – SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.