EU Risk Management Plan (RMP) for

Xerava

(eravacycline)

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP:	Amendment of indication to include use in adolescents.
Summary of significant changes in this RMP:	Update of indication to include use in adolescents (12 - 17 years) throughout the RMP. Reflecting newly approved SmPC wording on paediatric indication in routine risk minimisation measures Change of Marketing Authorisation Holder Update of post-authorisation exposure
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Date of approval:	

QPPV name: Dr. Leonardo Ebeling

QPPV signature:

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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ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immune deficiency syndrome
ALT	alanine transaminase
ANS	autonomic nervous system
APACHE II	acute physiology and chronic health evaluation II
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{last}	Area under the concentration-time curve up to the last measurable concentration
$AUC_{0\text{-}12h}$	Area under the concentration-time curve from time zero to 12 hours post-dose
BCRP	breast cancer resistance protein
BSEP	bile salt export pump
CDER	Center for Drug Evaluation and Research
C. difficile	*Clostridioides difficile*
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cIAI	complicated intra-abdominal infection
CIAO	Complicated Intra-Abdominal Infection Observational
CIAOW	Complicated Intra-Abdominal Infections Worldwide Observational
CLSI	Clinical & Laboratory Standards Institute
C_{max}	maximum observed plasma concentration
$C_{max,ss}$	maximum steady-state plasma concentration during a dosage interval
CMQ	company-defined medical query
CNS	central nervous system
COX	cyclooxygenase
CRAB	carbapenem-resistant *Acinetobacter baumannii*
CrCl	creatinine clearance
CSR	clinical study report
cUTI	complicated urinary tract infection
CYP	cytochrome P450
dL	decilitre
DLP	Data lock point
DNA	Deoxyribonucleic acid
EARS-Net	European Antimicrobial Resistance Surveillance Network
ECDC	European Centre for Disease Prevention and Control
ECG	electrocardiogram
EEA	European Economic Area

EMA	European Medicines Agency
EPAR	European Public Assessment Report
ESBL	extended-spectrum β-lactamase
ESRD	end-stage renal disease
EU	European Union
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration
FOB	functional observational battery
F_0	parent generation
F_1	first generation offspring of the parent generation
F_2	second generation offspring of the parent generation
GD	gestation day
GI	gastrointestinal
GLP	Good Laboratory Practices
h	hour(s)
HAP	hospital-acquired pneumonia
HEK293	human embryonic kidney cells
hERG	human ether-à-go-go-related gene
HIV	human immunodeficiency virus
IAI	intra-abdominal infection
IBD	International birth date
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICU	intensive care unit
IC_{50}	median (50%) inhibitory concentration
IDSA	Infectious Diseases Society of America
IgE	immunoglobulin E
IgG	immunoglobulin G
i.v.	intravenous
kg	kilogram
KLH	anti-keyhole limpet haemocyanin
L	litre
MAH	marketing authorisation holder
MATE	multidrug and toxin extrusion transporter
MATE1	multidrug and toxin extrusion transporter (MATE)1
MATE-2K	multidrug and toxin extrusion transporter (MATE)2-K
MBL	metallo-β-lactamase
MDR	multidrug resistant
MDR1	multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities

mg	milligram
MIC	minimum inhibitory concentration
min	minutes
mL	millilitre
mmHg	millimetre of mercury
mRNA	messenger ribonucleic acid
MRP1	multidrug resistance-associated protein 1
msec	millisecond
MTD	maximum tolerated dose
mtDNA	mitochondrial DNA
µg	microgram
µM or µmol	micromolar
µL	microlitre
NOAEL	no-observable-adverse-effect-level
NOEL	no-observable-effect-level
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OATP1B1	organic anion-transporting polypeptide 1B1
OATP1B3	organic anion-transporting polypeptide 1B3
OCT1	organic cation transporter 1
OCT2	organic cation transporter 2
OIE	World Organisation for Animal Health
OR	odds ratio
OXA	oxacillinase
PASS	post-authorisation safety study
PIP	Paediatric Investigation Plan
P-gp	p-glycoprotein
PK	pharmacokinetic(s)
PL	package leaflet
PND	post-natal day
p.o.	*per os*, oral, orally
PSUR	Periodic Safety Update Report
PT	preferred term
QPPV	Qualified person responsible for pharmacovigilance in the EU
QT	QT interval
QTc	Corrected QT interval
QTcB	QT interval corrected using Bazett's formula
QTcF	QT interval corrected using Fridericia's formula
QTcI	QT interval corrected for the individual patient
q12h	every 12 hours
Q2	second quarter

Q3	third quarter
q24h	every 24 hours
RMP	Risk Management Plan
RNA	ribonucleic acid
RPP	ribosome protection protein
rRNA	ribosomal ribonucleic acid
SMART	Study for Monitoring Antimicrobial Resistance Trends
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA query
TcdA	*Clostridioides difficile* toxin A
TcdB	*Clostridioides difficile* toxin B
TEAE	treatment-emergent adverse event
tet gene	tetracycline resistance gene
TOC	test of cure
TP-034	metabolite of TP-434
TP-434	eravacycline
TP-498	metabolite (C-4 epimer) of TP-434
TP-6208	metabolite of TP-434
TQT	thorough QT interval
ULN	upper limit of normal
US	United States
USA	United States of America
UTI	Urinary tract infection
VAP	vascular access port
WBC	white blood cell
WHO	World Health Organization
WISS	WSES cIAIs Score Study
WSES	World Society of Emergency Surgery

Part I: Product Overview

Table 1: Part I.1 – Product Overview

Active substance (INN or common name)	Eravacycline
Pharmacotherapeutic groups (ATC Code)	Antibacterials for systemic use, tetracyclines (J01AA13)
Marketing Authorisation Holder (MAH)	PAION Pharma GmbH
Medicinal products to which this RMP refers	Xerava 50 mg powder for concentrate for solution for infusion Xerava 100 mg powder for concentrate for solution for infusion
Invented name in the European Economic Area (EEA)	Xerava
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Eravacycline is a fluorocycline belonging to the tetracycline class of antibiotics.
	Summary of mode of action: The mechanism of action of eravacycline involves the disruption of bacterial protein synthesis by binding to the 30S ribosomal subunit thus preventing the incorporation of amino acid residues into elongating peptide chains. The C-7 and C-9 substitutions in eravacycline are not present in any naturally occurring or semisynthetic tetracyclines and the substitution pattern imparts microbiological activities including retention of *in vitro* potency against Gram-positive and Gram-negative strains expressing tetracycline-specific resistance mechanism(s) (i.e., efflux mediated by tet(A), tet(B), and tet(K); ribosomal protection as encoded by tet(M) and tet(Q)). Eravacycline is not a substrate for the MepA pump in *Staphylococcus aureus* that has been described as a resistance mechanism for tigecycline. Eravacycline is also not affected by aminoglycoside inactivating or modifying enzymes.
	Important information about its composition: <u>Xerava 50 mg powder for concentrate for solution for infusion:</u> Each vial contains 50 mg eravacycline. The contents of the required number of vials should each be reconstituted with 5 mL water for injections. Reconstituted Xerava should be a clear, pale yellow to orange solution. For administration, the reconstituted solution must be further diluted using sodium chloride 9 mg/mL (0.9%) solution for injection. The calculated volume of the reconstituted solution

	should be added to the infusion bag to a target concentration of 0.3 mg/mL, within a range of 0.2 to 0.6 mg/mL. Xerava 100 mg powder for concentrate for solution for infusion: Each vial contains 100 mg eravacycline. The contents of the required number of vials should each be reconstituted with 5 mL water for injections or with 5 mL sodium chloride 9 mg/mL (0.9%) solution for injection. Reconstituted Xerava should be a clear, pale yellow to orange solution. For administration, the reconstituted solution must be further diluted using sodium chloride 9 mg/mL (0.9%) solution for injection. The calculated volume of the reconstituted solution should be added to the infusion bag to a target concentration of 0.3 mg/mL, within a range of 0.2 to 0.6 mg/mL.
Hyperlink to the Product Information	Xerava Product Information (Module 1.3.1)
Indication in the EEA	Current: Xerava is indicated in adolescents from the age of 12 years weighing at least 50 kg, and in adults, for the treatment of complicated intra-abdominal infections (cIAI) Consideration should be given to official guidance on the appropriate use of antibacterial agents
	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose regimen is 1 mg/kg eravacycline every 12 hours for 4 to 14 days.
	Proposed: Not applicable
Pharmaceutical form and strengths	Current: Powder for concentrate for solution for infusion (powder for concentrate). Pale yellow to dark yellow cake. Xerava 50 mg powder for concentrate for solution for infusion: Each vial contains 50 mg eravacycline. Reconstituted Xerava should be a clear, pale yellow to orange solution. After reconstitution each mL contains 10 mg eravacycline. After further dilution 1 mL contains 0.3 mg eravacycline. Xerava 100 mg powder for concentrate for solution for infusion: Each vial contains 100 mg eravacycline.

	Reconstituted Xerava should be a clear, pale yellow to orange solution. After reconstitution each mL contains 20 mg eravacycline. After further dilution 1 mL contains 0.6 mg eravacycline.
	Proposed: Not applicable.
Is the product 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:

Xerava is indicated in adolescents from the age of 12 years weighing at least 50 kg, and in adults,for the treatment of complicated intra-abdominal infections (cIAI).

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

Complicated intra-abdominal infections (cIAIs) are infections that extend beyond the hollow viscus of origin into the peritoneal or retroperitoneal spaces and are associated with either abscess formation or peritonitis and systemic signs and symptoms of illness (Blot et al., 2005; Solomkin et al., 2010). They affect a variety of organs and diagnoses including intra-abdominal abscess, perforation of the stomach or intestine, peritonitis, appendicitis with perforation, periappendiceal abscess, cholecystitis with perforation or abscess, and diverticulitis with perforation, peritonitis or abscess (Marshall 2004; De Waele et al., 2008; Babinchak et al., 2005). Different bacterial pathogens are responsible for cIAIs, including Gram-negative aerobic bacteria, Gram-positive bacteria, and anaerobic bacteria, and there are also mixed infections (CDER 2015). Their treatment involves both surgical and antibiotic therapy and they are an important cause of morbidity, frequently associated with a poor prognosis and consume substantial hospital resources and costs (Blot et al., 2005; Sartelli et al., 2013; Solomkin et al., 2003).

Eravacycline is a novel, synthetic, broad-spectrum fluorocycline antibiotic that is highly active against bacterial pathogens causing cIAI. Eravacycline is active against clinically important multidrug resistant (MDR) Gram-negative and Gram-positive aerobic and anaerobic pathogens, including Enterobacteriaceae that produce extended-spectrum β-lactamases (ESBLs) and/or carbapenemases from all of the Ambler classes. Eravacycline is also unique among antimicrobials in late-stage development in that it possesses potent activity against carbapenem-resistant *Acinetobacter baumannii* (CRAB), including those with blaOXA carbapenemases and isolates displaying MDR (Sutcliffe et al., 2013).

Incidence and prevalence:

The incidence of cIAIs is difficult to determine because of its inclusion in a broad range of diagnoses (Townsend et al., 2007). There are multiple sources of infection as demonstrated in the World Society of Emergency Surgery [WSES] cIAIs Score Study (WISS), a multicentre observational worldwide study in 132 medical institutions over a four-month study period (October 2014 to February 2015) (Table 2; Sartelli et al., 2015). Appendicitis is the most frequent source of cIAI with appendicitis accounting for more than 44,000 hospital admissions in England every year (Humes et al., 2006).

In vitro susceptibility patterns of clinical Gram-negative bacilli to antimicrobial agents collected from IAIs to identify changes in resistance patterns in community- or hospital-acquired organisms, including those that produce ESBLs, were monitored in the worldwide Study for Monitoring Antimicrobial Resistance Trends (SMART) (Morrissey et al., 2013). Over the course of the SMART study from 2002 to 2011, the five most commonly isolated Gram-negative pathogens associated with IAIs (92,086 isolates) were *Escherichia coli* (47.8%), *Klebsiella pneumoniae* (14.5%), *Pseudomonas aeruginosa* (9.4%), *Enterobacter cloacae* (6.0%) and

Proteus mirabilis (3.6%). This was very similar across all geographical regions. The prevalence of ESBL producing pathogens in intra-abdominal infections was found to have steadily increased over time in Europe, Asia, Latin America, Middle East (all p<0.0001), North America (p=0.03) and South Pacific (p=0.009), but not in Africa where it decreased (p=0.037) (Morrissey et al., 2013).

Table 2: Source of infection in 4553 patients from 132 hospitals worldwide in the WISS study (World Society of Emergency Surgery [WSES] cIAIs Score Study) (15 October 2014 to 15 February 2015)[1]

Source of infection	Number of patients	Percentage of patients
Appendicitis	1553	34.2%
Cholecystitis	837	18.5%
Gastro-duodenal perforations	498	11.0%
Post-operative	387	8.5%
Colonic non diverticular perforation	269	5.9%
Small bowel perforation	243	5.4%
Diverticulitis	234	5.2%
Post traumatic perforation	114	2.5%
Pelvic inflammatory disease	50	1.1%
Others	348	7.7%
Total	4553	100%

[1]Sartelli et al., 2015

Demographics of the population in the proposed indication and risk factors for the disease:

There are multiple sources of cIAIs, thus patients of all ages and races are affected. In the multicentre European Complicated Intra-Abdominal Infection Observational (CIAO) study 2,152 patients were evaluated including 996 (46.3%) females and 1,156 (53.7%) males with a mean age of 53.8 years (range 4 to 98 years) (Sartelli et al., 2012). Among these patients, 1,701 (79%) were affected by community-acquired IAIs while the remaining 451 (21%) suffered from healthcare-associated infections. The most frequent (≥ 5%) sources of infection were appendicitis (n=798, 37%), cholecystitis (n=289, 13.4%), post-operative (n=342, 15.9%), colonic non-diverticular perforation (n=158, 7.3%), gastroduodenal perforations (n=156, 7.3%), and diverticulitis (n=166, 7.7%) (Sartelli et al., 2012).

The worldwide multicentre WISS study involving 4533 patients with a mean age of 51.2 years (range 18 to 99 years) was comprised of 1935 (42.7%) women and 2598 (57.3%) men with an overall mortality rate of 9.2% (416/4533) (Sartelli et al., 2015). Among these patients, 3966 (87.5%) were affected by community-acquired IAIs while the remaining 567 (12.5%) suffered from healthcare-associated infections. The various sources of infection in this study are presented in Table 2. The most frequent source of infection was acute appendicitis with 1553 cases (34.2%) involving complicated appendicitis. Seven hundred ninety-one patients (17.4%) were admitted in a critical condition (severe sepsis/septic shock).

Factors increasing a patient's risk for a poor outcome from cIAIs include advanced age (>70 years), immunosuppression (poor nutritional status, corticosteroid therapy, organ transplantation), presence of malignancy and pre-existing chronic conditions (liver disease,

renal disease), and disease-specific factors including a high acute physiology and chronic health evaluation II (APACHE II) score (>15), health care-associated infection, delay in initial intervention (>24 h) and inability to obtain source control (Shirah and O'Neill 2014).

Hospitalisation is a recognised risk factor for developing a cIAI. The microbiology of IAIs may be altered in patients who have been exposed to the healthcare setting due to the acquisition of nosocomial pathogens or may reflect prior antimicrobial therapy that has selected for resistant organisms (Mazuski and Solomkin 2009). Compared with patients who have community-acquired IAIs, patients who have acquired their IAIs postoperatively have a shift in the relative frequency of the Gram-negative isolates, with *E. coli* and *Streptococci* being isolated less often, whereas *Enterobacter*, *Pseudomonas* and *Enterococcus* are more often (Mazuski and Solomkin 2009).

The main existing treatment options:

Effective management of cIAIs requires the timely institution of appropriate antimicrobial therapy and, in most cases, surgical interventions (Solomkin et al., 2003). The choice of antimicrobial therapy for IAI depends on the severity of the illness, whether the infection was community- or hospital-acquired, and the history of bacterial resistance in the hospital and community (Solomkin et al., 2003).

The major pathogens involved in community-acquired IAIs are usual residents of the gastrointestinal tract, including Enterobacteriaceae, streptococci, and certain anaerobes (particularly *Bacteroides fragilis*). Healthcare-associated IAIs are commonly caused by a more resistant flora, which may include *Acinetobacter* spp., ESBL-producing *K. pneumoniae* and *E. coli*, carbapenemase-producing *K. pneumoniae*, enterococci, *P. aeruginosa* and *Candida* spp (Brook et al., 2000; Coates et al., 2005; Sartelli et al., 2012).

Historically, patients with community-acquired IAI have received narrower-spectrum agents that provide coverage against the common Gram-negative and Gram-positive aerobic and obligate anaerobic microorganisms typically found with these infections (Mazuski and Solomkin 2009). In contrast, patients who have nosocomial IAIs, may benefit from a broader-spectrum empiric regimen, which includes selective use of agents effective against resistant Gram-negative organisms, *Enterococcus* spp., and *Candida* spp. However, this is changing as the prevalence of drug-resistant and multidrug resistant bacterial pathogens increases in the community setting.

In 2010 evidence-based guidelines for managing patients with cIAI were prepared by an Expert Panel of the Surgical Infection Society and the Infectious Diseases Society of America (IDSA) (Solomkin et al., 2010). In response, a panel of European experts from surgery, intensive care, clinical microbiology and infectious diseases developed recommendations for cIAIs (Eckmann et al., 2011). They recommend that choosing the right antibiotics for a particular patient should be influenced by a multitude of factors including patient factors (co-morbidities, immunosuppression, previous antimicrobial treatment), expected microbial spectrum, local bacterial and resistance statistics, ease of application, level of toxicity and costs (Eckmann et al., 2011).

The appropriate use of antimicrobials is essential for reducing and preventing antimicrobial resistance. Infections due to MDR organisms are difficult to treat and eradicate because they do not respond to many common antibiotics, and in some cases do not respond to even the most powerful agents, such as carbapenems. The carbapenems are becoming less effective because carbapenemases and porin changes that mediate resistance have become more common, even in enteric bacteria. Enterobacteriaceae, *Pseudomonas*, and *Acinetobacter* species are more

likely than others to develop MDR. The recent emergence of carbapenem-resistant Enterobacteriaceae is a major threat to hospitalised patients. In the CIAO Study, ESBL producers were the most commonly identified drug-resistant microorganisms involved in IAIs with ESBL-producing *E. coli* isolates comprising 10.1% (64/632) of all *E. coli* isolates, while ESBL-positive *K. pneumoniae* isolates represented 33.9% (37/109) of all *K. pneumoniae* isolates (Sartelli et al., 2012). Many factors can increase the likelihood of ESBL involvement in IAIs including excessive use of antibiotics, residence in a long-term care facility, and recent hospitalisation (Sartelli et al., 2012).

Antimicrobial resistance data from invasive isolates reported to the European Antimicrobial Resistance Surveillance Network (EARS-Net) by 29 EU/EEA countries highlighted the significant increase in resistance to cephalosporins in *K. pneumoniae* and *E. coli* at both EU/EEA level as well as in many individual member states over the last four years (2011-2014) (ECDC 2015). A large proportion of the isolates resistant to third-generation cephalosporins produced an ESBL. Third-generation cephalosporin resistance was often seen in combination with fluoroquinolone and aminoglycoside resistance. The EU/EEA trend for this type of combined resistance increased significantly between 2011 and 2014 for both *E. coli* and *K. pneumoniae*.

Acinetobacter spp. resistance to a combination of three antimicrobial classes (fluoroquinolones, aminoglycosides and carbapenems) was as high as 47.8% (1,870 of 3,910 isolates tested) in EU and EEA countries in 2014 (ECDC 2015). Treatment options for MDR *Acinetobacter* infections are currently so limited that clinicians are forced to use older, previously discontinued, drugs such as colistin, that are associated with significant renal toxicity and for which there is a lack of robust data to guide proper selection of dosage regimen or duration of therapy (Maragakis et al., 2008). Even a recently approved new formulation of a legacy tetracycline (minocycline i.v.), offers some *Acinetobacter* coverage, but due to pre-existing resistance, does not provide complete coverage (Zilberberg et al., 2016; He et al., 2015).

Although a wide range of individual antimicrobial agents and combinations of agents are available for use in cIAI, no regimen to date has been consistently demonstrated to be superior. Few cover all the potential pathogens to which the peritoneum is exposed following a perforation of the intestinal tract. Thus, there is a need for broad-spectrum antibiotics with appropriate pharmacokinetics to empirically cover the wide range of potential pathogens seen in cIAIs and which, importantly, show efficacy against MDR organisms (WHO 2014).

Tigecycline, a parenteral glycylcycline antibiotic derived from minocycline authorised in the EU in April 2006, is a useful treatment option for cIAI due to its favourable *in vitro* activity against anaerobic organisms, enterococci, several ESBL- and carbapenemase-producing Enterobacteriaceae, and *Stenotrophomonas maltophilia*, although it has limited *in vitro* activity against *P. aeruginosa* or *P. mirabilis* (Sartelli et al., 2013). Tigecycline is able to overcome the two major tetracycline resistance mechanisms, ribosomal protection and efflux but tigecycline is vulnerable to chromosomally-encoded multi-drug efflux pumps of Proteeae and *P. aeruginosa* (Tygacil SmPC). In Europe there is a wide heterogeneity in clinical practice with use of tigecycline as monotherapy for cIAI varying from 18.2% to 95.7% across four European countries evaluated (Germany, Italy, France and Spain), with some countries preferring the use of tigecycline as combination therapy, often paired with third- or fourth-generation cephalosporins (Eckmann et al., 2013). However, despite heterogeneity in antibiotic use, clinical cure rates with tigecycline were found to be similar across the different healthcare systems, local microbiological environments, treatment modalities and prescription behaviours (Eckmann et al., 2013).

Combination antibiotics are often used in clinical practice such as piperacillin/tazobactam. Two new β-lactam/β-lactamase inhibitor combinations, ceftolozane/tazobactam and ceftazidime/avibactam, have been approved recently but neither has activity against metallo-β-lactamases, an important class of enzymes with carbapenemase activity, and both lack complete coverage of class A, C and D enzymes (Bush 2015; Winkler et al., 2015; Berrazeg et al., 2015; Castanheira et al., 2014; Shields et al., 2015).

The carbapenems, used against MDR bacteria, are members of the β-lactam class of antibiotics. Ertapenem has a broad spectrum of *in vitro* activity against Gram-negative pathogens, including ESBL- and AmpC-producing Enterobacteriaceae, Gram-positive pathogens and anaerobic pathogens (Bai et al., 2014). It has similar efficacy to ceftriaxone in complicated infections such as cIAI, cUTI and community-acquired pneumonia. With a convenient once-daily administration schedule and well-tolerated safety profile, ertapenem has widespread use for the empiric treatment of community-acquired cIAI (Solomkin et al., 2003; Namias et al., 2007; De Waele et al., 2013). It is also associated with a lower rate of bowel colonisation with resistant Enterobacteriaceae in IAI when compared with piperacillin/tazobactam (DiNubile et al., 2005) and has reduced activity against *P. aeruginosa*. Antipseudomonal carbapenems include imipenem and meropenem that exert their bactericidal activity by inhibiting bacterial cell wall synthesis in Gram-positive and Gram-negative bacteria through binding to penicillin-binding proteins.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Intra-abdominal infections comprise many pathological conditions including uncomplicated and complicated IAIs and are classified into community-acquired IAIs and IAIs that develop in hospitalised patients or residents of long-term care facilities, the latter characterised by increased mortality (Menichetti and Sganga 2009; Sartelli 2010; Pieracci and Barie 2007).

Untreated cIAIs have a significant impact on morbidity and mortality. As the infection progresses, the patient can develop sepsis, multi-organ failure and death if not treated with an effective antibiotic with or without surgery. Even with treatment, cIAIs represent an important cause of morbidity and are frequently associated with poor prognosis (Sartelli 2010).

Patients with infections due to resistant organisms are at higher risk for treatment failure and death (Mazuski and Solomkin 2009). In the European CIAO study a mortality rate of 7.6% (163/2,152 patients) was observed (Sartelli et al., 2012). Similarly, a mortality rate of 10.5% (199/1898) was found in the Complicated Intra-Abdominal Infections Observational Worldwide (CIAOW) study, a multicentre observational study of adult patients undergoing surgery or interventional drainage to address cIAIs in 68 medical institutions worldwide from October 2012 to March 2013 (Sartelli et al., 2014). Significant risk factors for death during hospitalisation included the clinical condition upon hospital admission (including severe sepsis, septic shock, healthcare associated infection), the source of infection (including colonic non-diverticular perforation, small bowel perforation, complicated diverticulitis, post-operative infections, delayed initial intervention), the immediate post-operative course (severe sepsis, septic shock, ICU admission) and co-morbidities (malignancy, immunosuppression, serious cardiovascular disease). A delayed initial intervention (a delay exceeding 24 hours) was associated with an increased mortality rate (OR=3.6; 95% CI: 1.9; 3.7; p<0.0001) (Sartelli et al., 2014).

Important co-morbidities:

There are no important co-morbidities specific to the target population with cIAI.

In a population-based, retrospective cohort study in the Netherlands of IAIs, the most frequent concomitant diseases were cardiovascular, pulmonary and immunomodulatory in 175 cases (Sturkenboom et al., 2005). Important co-morbidities were highlighted by their association with mortality. In this study mortality was associated with increasing age (all deaths were in those >65 years of age, p<0.001), cardiovascular co-morbidity (p=0.013), endocrinological co-morbidity (p=0.003), and origin of infection (highest risk for upper gastrointestinal tract origin [15.4%], 6.4% for lower GI and 1.1% for appendix as origin, p=0.016). Meanwhile in the CIAOW study, patient co-morbidities associated with patient mortality included malignancy (odds ratio [OR] = 3.6; 95% CI: 2.5; 15.1; p<0.0001), and serious cardiovascular disease (OR=4.5; 95% CI: 3.2; 6.3; p<0.0001) (Sartelli et al., 2014). In this study the co-morbidity immunosuppression was found to be an independent predictor of mortality during hospitalisation with an elevated OR (OR=3.8; 95% CI: 2.1-6.7; p < 0.0001) (Sartelli et al., 2014).

The patient population includes a wide range of patients covering various co-morbidities, and there are no concomitant medications that would typically be administered to the target population. Patients with cIAIs are likely to be receiving multiple co-medications to alleviate their symptoms associated with their infections, such as fever and pain, and in case of disease progression sepsis, tachycardia, acidosis and extra-abdominal organ fever. Treatment for their underlying condition is also expected.

Part II: Module SII - Non-clinical part of the safety specification

Eravacycline has been evaluated in a comprehensive non-clinical program to assess the toxicology of eravacycline, including evaluation of metabolites, impurities, and degradants (Module 2.4, Non-clinical Overview).

Single-dose toxicity studies have been conducted in the rat, dog, and monkey with i.v. administration of eravacycline. Eravacycline was evaluated in pivotal repeat dose toxicity studies following i.v. administration over dose ranges up to 40 mg/kg/day in rats, 20 mg/kg/day in dogs, and 18 mg/kg/day in cynomolgus monkeys for up to 13 weeks, 14 days, and 13 weeks in duration, respectively. The rat and the monkey were selected as the species of choice for the i.v. eravacycline non-clinical development program as eravacycline metabolism is similar to humans with regards to formation of the TP-6208 metabolite. High doses of eravacycline produced overt cutaneous histamine-like signs in rats and dogs within minutes of i.v. administration; the dog was intolerant to these histamine-like effects. These signs were not apparent in monkeys.

A comprehensive battery of reproductive and developmental toxicity studies in rats and rabbits assessed the potential effects of eravacycline following i.v. administration. In addition, dose range finding and pivotal juvenile toxicity studies in rats were conducted to support the use of eravacycline in a paediatric population in accordance with the approved Paediatric Investigational Plan (PIP) (EMEA-001555-PIP01-13-M04).

Eravacycline has been evaluated in a complete battery of *in vitro* and *in vivo* genetic toxicity studies. Computational assessments and genotoxicity studies were completed for eravacycline, plus its intermediates, degradants, starting materials, metabolites, and impurities.

The carcinogenic potential of eravacycline has not been evaluated based on the short-term, intermittent use of the drug.

Additional studies with eravacycline included local tolerance, inhibition of mitochondrial DNA encoded protein synthesis, phototoxic potential, and haemocompatability.

Toxicity assessments were performed to qualify the major human metabolites (TP-498, TP-6208 and TP-034) and the eravacycline impurities (process impurities, degradation products, intermediates, or starting materials). TP-498, TP-6208 and TP-034 were also investigated in CYP inhibition/induction studies and transporter studies with the relevant findings presented in the Xerava Summary of Product Characteristics (Xerava SmPC). No guidance concerning the impurities and degradants is needed for the use of eravacycline in clinical practice.

Table 3: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity	
Acute or repeat-dose toxicity studies Doses of ≥25 mg/kg eravacycline as a single i.v. bolus injection in the rat resulted in lethargy, laboured breathing, and redness of the limbs and ears; symptoms consistent with a transient histamine-like reaction. In a second rat study discolouration of the tail, apparent blood in urine, and histamine-like symptoms consisting of erythema of ears/paws; swelling of nose/paws/ears; red material around eyes/nose; salivation; decreased	The main treatment related effects in the rat and dog were largely regarded as secondary to histamine intolerance. The transient histamine-like response has been observed with other tetracycline compounds (e.g., tigecycline), and therefore was not unexpected. Tetracyclines induce histamine release in rats and dogs, but not in primates or humans. In the clinical development programme the main toxicities with eravacycline treatment were

Key Safety findings (from non-clinical studies)	Relevance to human usage
activity; pale mucous membranes, ataxia, and dyspnoea were observed. Administration of 75 mg/kg eravacycline resulted in mortality. In dogs, eravacycline was associated with hives after each dose which were widespread at 25 mg/kg. Swelling around the eyes, stereotypic activity, lethargy, salivation, emesis, observation of warm to touch, and struggling during dosing were also observed in males and females. The maximum tolerated dose (MTD) was 15 mg/kg in the male dog and 25 mg/kg in the female dog with a single i.v. bolus of eravacycline. In the 14-day i.v. toxicity studies, administration of eravacycline 40 mg/kg/day in the rat, ≥12 mg/kg/day in the dog, and 18 mg/kg/day in the cynomolgus monkey was not well tolerated resulting in moribundity, overt clinical signs (histamine-mediated clinical signs in rats and dogs; emesis and faecal abnormalities in dogs and monkeys; dehydration, and/or generalised deterioration in clinical condition in all animal species), body weight loss, decreases in food consumption, and associated clinical pathology alterations. Microscopic findings included changes in the following: gastrointestinal tract (dog and monkey), bone marrow and lymphoid tissues (rat, dog, and monkey), male reproductive system (rat), and heart (dog). In the 13-week repeat-dose toxicity studies, the no-observable-adverse-effect-level (NOAEL) was 4 mg/kg/day in cynomolgus monkeys (i.v. eravacycline; dose levels of 0, 1, 2, 4, and 8 mg/kg/day) corresponding to a margin over human exposure of 5.2 for eravacycline, 16 mg/kg/day in female rats and 4 mg/kg/day in male rats (i.v. eravacycline; dose levels of 0, 2, 4, 8, and 16 mg/kg/day) corresponding to margins over human exposure of 2.3 and 18.9 for eravacycline respectively. Toxicity in the rat and monkey were similar with the exception that the rat had male reproductive findings, and the monkey did not experience the histamine response. Histopathological findings in the 2 principal toxicology animal species (rat, and monkey) included changes in the gastrointestinal tract (monkey), the bone marrow and lymphoid tissues (rat, and monkey), and the male reproductive system (rat). Most findings were concluded to be related to the pharmacological manifestations of histamine intolerance.	gastrointestinal in nature comprising nausea, vomiting and diarrhoea. They were mainly mild to moderate in severity and occurred early in the treatment schedule, with very few events leading to discontinuation of eravacycline. These are known adverse effects of the tetracycline class. Hypersensitivity was reported in the Phase 3 cIAI Study TP-434-008. Two subjects in the eravacycline group experienced moderate hypersensitivity events. One event was assessed as probably related and the other event was assessed as not related to study drug. These isolated events described as ‘allergic reaction’ and ‘allergy symptoms’ remained local to the puncture site and there was no reported urticaria. A severe hypersensitivity reaction was observed in a subject treated with eravacycline in Phase 3 cUTI Study TP-434-021. Ten minutes after the infusion started the subject became nervous and had a heating sensation in the torso and neck. He experienced difficulty breathing, a pressure sensation in the chest and was relatively hypotensive. Eravacycline treatment was withdrawn and the subject treated with supplemental oxygen, chloropyramine, methylprednisolone, serum glucose 5% and aminophylline. The subject recovered. The hypersensitivity reaction was assessed as definitely related to study drug. Hypersensitivity is a recognised adverse reaction of eravacycline. The Xerava SmPC advises that serious and occasionally fatal hypersensitivity reactions are possible and have been reported with other tetracycline class antibiotics and that in case of hypersensitivity reactions, treatment with eravacycline must be discontinued immediately and appropriate emergency measures must be initiated. Overall the toxicities observed in the single and repeat-dose toxicity studies are not of significance for use of eravacycline in humans.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Reproductive/developmental toxicity Effects on the male reproductive system were observed in the 14-day i.v. rat toxicity study. Treatment-related organ weight changes with microscopic correlates were present in the prostate and seminal vesicles of 40 mg/kg/day males. Decreased epididymis and testis weights were observed at 20 or 40 mg/kg/day. At 40 mg/kg/day eravacycline gross pathological findings with microscopic correlates were found in the prostate and seminal vesicles with degeneration of seminiferous tubules, oligospermia and cellular debris in the epididymides. Reduced effects were also observed in the 20 mg/kg/day males. Similar effects on the male reproductive system were observed during the 13-week i.v. rat toxicity study with complete recovery of organ weights and microscopic findings during the 7-week recovery period. In male rats the NOAEL was 4 mg/kg/day eravacycline. No effects on reproductive organs in female rats were observed in the repeat-dose toxicity studies. No effects on reproductive organs were observed in either sex in the monkey repeat-dose toxicity studies. In a male rat fertility study (0, 1, 4, 12, and 16 mg/kg/day), reduced sperm counts and reduced fertility were observed following repeat i.v. doses of 12 and 16 mg/kg/day of eravacycline. All male reproductive findings were reversible at 12 and 16 mg/kg/day following a 50-day recovery period. The male toxicity and fertility NOAELs were 4 mg/kg/day eravacycline. In the female rat fertility study (0, 4, 8, and 20 mg/kg/day) fertility was unaffected at 20 mg/kg/day. The maternal toxicity and female reproductive NOAELs were 8 and >20 mg/kg/day, respectively. A definitive rat embryo-foetal development study was conducted using eravacycline co-administered with TP-6208, the primary eravacycline metabolite observed in humans, dogs, and monkeys, which is present only in small quantities in rats. In embryo-foetal toxicology studies, the maternal and developmental NOAEL was 5 mg/kg/day in the rat (0, 3.5/3, 0/5, 3.5/5, and 3.5/10 mg/kg/day TP-6208/eravacycline) and 2 mg/kg/day in the rabbit (0, 1, 2, or 4 mg/kg/day). In a perinatal and postnatal toxicology study in rats (0, 3, 5, or 10 mg/kg/day), matings were unremarkable, and no external abnormalities were seen in the second (F_2) generation foetuses. The parental (F_0) generation toxicological NOAEL was	**Pregnancy** In the clinical development programme there was no exposure of eravacycline in patients with cIAI who were pregnant or became pregnant while receiving eravacycline. However there have been 2 cases of eravacycline exposure during pregnancy in Phase 3 Study TP-434-010 in which eravacycline was evaluated for the treatment of cUTI, including one pregnancy that was electively terminated 6 weeks after starting eravacycline and the other pregnancy resulted in a healthy child. As use of eravacycline during pregnancy is limited, the safety of eravacycline during pregnancy is considered unknown. Tetracycline class antibiotics are recognised to cause permanent dental defects (discolouration and enamel defects) and a delay in ossification processes in the foetus if the mother is exposed during the 2nd or 3rd trimester of pregnancy or in the child during tooth development due to the accumulation in tissues with a high calcium turnover and formation of calcium chelate complexes. Therefore, there is a warning in the Xerava SmPC that eravacycline should not be used during pregnancy unless the clinical condition of the woman requires treatment with eravacycline. **Fertility** There are no human data on the effect of eravacycline on fertility. The Xerava SmPC informs healthcare professionals that eravacycline did affect mating and fertility in male rats at clinically relevant exposures. Eravacycline is not expected to adversely affect fertility in humans. **Lactation** It is unknown whether eravacycline and its metabolites are excreted in human breast milk. Long-term use of other tetracyclines during breast-feeding may result in significant absorption by the breast-fed infant and is not recommended because of the theoretical risk of dental discolouration and delay in ossification processes of the breast-fed infant. This guidance is reflected in the Xerava SmPC. Healthcare professionals are advised that a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Xerava should be made, taking into account the benefit of breast-feeding for the child, and the benefit of therapy for the woman. 'Permanent teeth discolouration and a delay in ossification processes (foetal exposure in

Key Safety findings (from non-clinical studies)	Relevance to human usage
5 mg/kg/day eravacycline, and both the F_0 generation reproductive NOAEL and the first (F_1) generation NOAEL for viability, growth, and reproduction were 10 mg/kg/day eravacycline. In a juvenile (post-natal day [PND] 21 at first dose) rat i.v. toxicology study (0, 4, 20, and 40 mg/kg/day), eravacycline, administered to male and female rats from PND 21 to 70 at doses of 20 and 40 mg/kg/day, produced microscopic findings in the male reproductive tract that reversed by the end of the recovery period. The NOAEL was 4 mg/kg/day in male rats and 20 mg/kg/day in female rats. Placental transfer of eravacycline and the metabolites TP-498, TP-6208, and TP-034 was evaluated in the rat and rabbit embryo-foetal development studies following i.v. administration to pregnant dams and does on Gestation Day (GD) 7 to 17 and GD 7 to 19, respectively. The presence of eravacycline, TP-498, TP-6208, and TP-034 (one animal) were confirmed in rat and rabbit foetal blood but not at all the lower doses administered. In the rabbit embryo-foetal study 4 mg/kg/day eravacycline resulted in abortion, adverse clinical observations, and reduced body weight gain and food consumption during the dosing period in the does and was associated with late resorptions, reduced foetal body weights, and delayed skeletal ossification. The maternal and developmental NOEL was 2 mg/kg/day eravacycline. Similar to other tetracyclines, eravacycline, TP-498, and TP-6208 were detected in milk on PND 15 following i.v. eravacycline to rats.	pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)' is considered an important potential risk with eravacycline (Module SVII).
Genotoxicity Eravacycline was not genotoxic in a standard battery of *in vitro* and *in vivo* assays (bacterial reverse mutation [Ames] assay, mouse lymphoma assay, human peripheral lymphocyte chromosomal aberration assay, or a rat bone marrow micronucleus study). Genotoxicity studies were also conducted to qualify metabolites and impurities. None of the metabolites nor impurities were found to be genotoxic.	None.
Carcinogenicity No carcinogenicity studies were conducted with eravacycline due to the short duration of proposed therapeutic use and because the results of genotoxicity testing did not reveal a relevant risk for humans. This is in accordance with ICH S1A *Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals* (November 1995).	None.

Key Safety findings (from non-clinical studies)	Relevance to human usage
Nephrotoxicity No nephrotoxic findings of significance were found in the non-clinical programme.	None. Eravacycline is not recognised to be nephrotoxic.
Hepatotoxicity No hepatotoxic findings of significance were found in the non-clinical programme.	None. Eravacycline is not recognised to be hepatotoxic.
Safety pharmacology	
Cardiovascular system (including potential effect on the QT interval) The effect of eravacycline on the human ether-à-go-go-related gene (hERG) channel current (a surrogate for IKr, the rapidly activating, delayed rectifier cardiac potassium current) was evaluated. Human embryonic kidney cells (HEK293 cells) were stably transfected with hERG complementary DNA. Eravacycline inhibited hERG potassium current by 0.9 ± 0.6% at 9.2 µM (n = 3), 5.6 ± 2.5% at 17.8 µM (n = 4), 8.3 ± 2.3% at 22.2 µM (n = 3), and 6.9 ± 1.1% at 91.6 µM (n = 3) compared to 0.4 ± 0.2% (n = 3) for buffer control. The IC_{50} of eravacycline for inhibition of hERG potassium current could not be calculated, but was estimated to be >22.2 µM, equivalent to >14.0 µg/mL. This concentration is higher than that achieved at the intended clinical dose; the mean C_{max} of eravacycline was 1.29 µg/mL following the Day 4 i.v. infusion of 1.0 mg/kg eravacycline twice daily in Study TP-434-006. Non-naïve male beagle dogs previously instrumented with radiotelemetry devices and iliac based vascular access ports (VAPs) were administered single dose 0, 5, 15, and 30 mg/kg eravacycline as 30-min i.v. infusions via a syringe pump connected to the animal's venous VAP. Skin clinical signs corresponding to acute histamine-like reactions, increased in frequency and severity in a dose dependent manner with 5, 15 and 30 mg/kg eravacycline. The higher doses (15 and 30 mg/kg) were associated with increases in heart rate, blood pressure, respiratory rate, and core body temperature, with corresponding quantitative changes in ECG. The changes were mild and transient and were not considered adverse. The NOEL for haemodynamic and respiratory parameters and ECG activity was 5 mg/kg eravacycline, which correlates to an eravacycline C_{max} of 5.45 µg/mL and an AUC_{last} of 15.5 µg·h/mL. The mean C_{max} of eravacycline was 1.29 µg/mL and the AUC over a 24h period was 9.12 µg·h/mL (AUC_{0-12} was 4.56 µg·h/mL) following	The exposures in the dog, especially at the higher doses, were greater than those observed in the thorough QT interval (TQT) study TP-434-004 in healthy subjects, where the mean C_{max} of eravacycline and its metabolites TP-498 and TP-6208 was 2.34, 0.079, and 0.107 µg/mL, respectively, and the highest C_{max} was 3.36, 0.148, and 0.369 µg/mL, respectively, after a single 60 min infusion of eravacycline at 1.5 mg/kg. In this TQT study, there was no evidence of a clinically significant QTc prolongation following administration of 1.5 mg/kg eravacycline. No subject had a QTcI interval >480 msec or a QTcI change from pre-dose >30 msec at any post-dose timepoint following a single i.v. 1.5 mg/kg dose of eravacycline. No subject had a QTcF or QTcB interval >480 msec or change from pre-dose >60 msec following eravacycline. In the eravacycline clinical studies there were no remarkable trends for ECG intervals and rates with eravacycline. Eravacycline is not recognised to be cardiotoxic.

Key Safety findings (from non-clinical studies)	Relevance to human usage
the Day 4 i.v. infusion of 1.0 mg/kg eravacycline twice daily in Study TP-434-006. There was no evidence of an adverse effect on core body temperature, QTc prolongation, mean arterial pressure, or respiratory parameters in these studies.	
Central nervous system (CNS) A functional observational battery (FOB) assessment was performed within 5 min after slow bolus i.v. eravacycline (0, 4, 30 and 60 mg/kg) and at 24 hours post-dose in male and female rats. Doses of 30 and 60 mg/kg were associated with laboured breathing, swelling, and skin erythema and changes in CNS activity and excitability (including reduction in rearing counts and activity/arousal and instances of muscle fasciculation) and effects on the autonomic nervous system (ANS), sensorimotor system, neuromuscular system (including ataxia and gait pattern abnormalities), and decreased body temperature. Some of these changes were severe, but all were transitory. At the 24 hour FOB time point all eravacycline dosed animals were comparable to the control animals. The findings observed may correspond to a secondary manifestation of a suspected histamine release like reaction caused by eravacycline. The NOEL in rats following a single i.v. injection was 4 mg/kg eravacycline.	There is no evidence of significant neurotoxicity in humans. Histamine release-like reactions do not occur in man.
Mechanisms for drug interactions	
Pharmacokinetic drug interactions The potential for eravacycline and its three human major metabolites (TP-498, TP-6208, and TP-034) to inhibit or induce the major CYP enzymes was evaluated in human liver microsomes and cultured human hepatocytes. In CYP inhibition (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) and induction (CYP1A2, CYP2B6, and CYP3A4) studies, neither eravacycline nor TP-6208 induced or was a direct or time-dependent or metabolism-dependent inhibitor of microsomal P450 enzymes. There was no time-dependent or metabolism-dependent inhibition of the major CYP enzymes by TP-498, but TP-498 caused a metabolism-dependent (24% increase) inhibition of CYP3A4/5-mediated testosterone 6β-hydroxylation, but not inhibition of a second CYP3A4/5 substrate, midazolam. The IC_{50} value for all the enzymes was >100 µM (equivalent to 56.2 µg/mL), the highest concentration of TP-498 tested. This IC_{50} value is 511-fold greater than the C_{max} (0.11 µg/mL) of TP-498 achieved clinically following i.v. dosing with 1	Eravacycline and its metabolites are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 *in vitro*, nor are they inducers of CYP1A2, CYP2B6 or CYP3A4. Interactions with medicinal products that are substrates for these enzymes or transporters are therefore unlikely. Eravacycline is not an inhibitor of the major human uptake or efflux transporters *in vitro* and therefore co-administration is unlikely to affect the uptake of concomitantly administered drugs which rely on these transporters. Eravacycline, TP-498 and TP-6208 are not inhibitors of BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT1, OCT2, MATE1 or MATE2-K transporters. The metabolites TP-498 and TP-6208 are not inhibitors of P-gp *in vitro*. Eravacycline is a substrate for the transporters P-gp, OATP1B1 and OATP1B3 but not for BCRP. Concomitant administration of the strong CYP 3A4/3A5 inducer rifampicin altered the pharmacokinetics of eravacycline decreasing exposure by approximately 32% and increasing clearance by approximately 54%. The eravacycline

Key Safety findings (from non-clinical studies)	Relevance to human usage
mg/kg eravacycline twice daily. TP-498 did not induce CYP activity or mRNA levels. Enzyme induction studies conducted in 3 cultures of human hepatocytes treated with TP-034 at concentrations ≥ 120 plasma $C_{max,ss}$ suggested that TP-034 had no potential to cause clinically relevant induction of CYP1A2. However, TP-034 may have the potential to cause clinically relevant induction of CYP2B6 and CYP3A4. Eravacycline did not inhibit (>20%) BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OCT1, OCT2, multidrug and toxin extrusion 1 (MATE1), or MATE2-K mediated transport. However, MDR1 (P-gp), OATP1B3, and OAT3 activity was inhibited by eravacycline at 20 µg/mL. TP-6208 did not inhibit any transporter at concentrations up to 10 µg/mL. TP-034 was shown to cause no clinically relevant inhibition of any of the 11 transporters examined and was identified as a potential substrate for the efflux transporters P-gp, BCRP, and BSEP. Eravacycline was a substrate of P-gp (0.4 µM concentration only) when eravacycline was incubated with MDCKII-P-gp cells for 2 hours. Under these conditions, the efflux ratio was > 2 and was inhibited by ≥ 50% by the P-gp inhibitor valspodar, but inhibition was < 50% with the P-gp inhibitor verapamil. Eravacycline was also determined to be a substrate of OATP1B1 (0.4 µM and 4 µM) and OATP1B3 (0.4 µM concentration only) after incubation with HEK293 cells expressing the relevant transporter for 1 min, since the uptake ratio was > 2 and was inhibited by ≥ 50% by the OATP1B1 and OATP1B3 inhibitors rifampicin and cyclosporine. Eravacycline appears to quickly saturate OATP1B1 and OATP1B3 transporters. Eravacycline was not a substrate of BCRP.	dose should be increased approximately 50% (1.5 mg/kg IV q12h) when co-administered with rifampicin or other strong CYP3A inducers such as phenobarbital, carbamazepine, phenytoin and St. John's Wort. In patients co-administered strong CYP3A4 inducers the recommended dose regimen is 1.5 mg/kg eravacycline every 12 hours for 4 to 14 days. Concomitant administration of the strong CYP3A inhibitor itraconazole altered the pharmacokinetics of eravacycline increasing C_{max} by approximately 5% and AUC_{0-24} by approximately 23%, and decreasing clearance. The increased exposure is not likely to be clinically significant; thus, no dose adjustment is required when eravacycline is co-administered with CYP3A inhibitors. However, patients receiving strong CYP3A inhibitors with a combination of factors that may increase the exposure, such as severe hepatic impairment and/or obesity should be monitored for adverse reactions. No important drug interactions were identified in the clinical development programme or are considered likely with eravacycline based on the drug interaction studies.
Other toxicity-related information or data	
Local tolerance Local tolerance effects of eravacycline were evaluated in the New Zealand White rabbit. Intravenous infusion of eravacycline once daily over 30 minutes for 3 days was well tolerated in rabbits. There were no treatment-related findings at 0.2, 0.4, and 1.0 mg/mL. Histopathological changes related to inflammation were slightly greater in incidence and severity at 5.0 mg/mL compared to the vehicle control. The incidence and severity of vascular/perivascular inflammation following i.v. eravacycline twice	In the Phase 2 and Phase 3 cIAI studies treatment-related AEs meeting the Infusion Site Complications company-defined medical query (CMQ) criteria occurred in 6.8% of subjects treated with eravacycline. The most frequently reported treatment-related events included phlebitis, infusion site phlebitis, and infusion site thrombosis. There were no serious or severe events. Across the safety population, no subjects discontinued eravacycline due to these events. These events are expected and are manageable in the clinical setting.

Key Safety findings (from non-clinical studies)	Relevance to human usage
daily at 5, 10, or 20 mg/mL with a 2-hour interval between the 60- and 30-minute infusions was similar in all groups. There were no differences in inflammatory changes at the injection site that were related to the concentration or rate of infusion of eravacycline in this study. Local tolerance was also evaluated in the pivotal repeat-dose i.v. toxicity studies by both gross and microscopic assessment of the injection sites. Injection site findings were observed specifically at higher concentrations of eravacycline, when a catheter or vascular access port was not utilised for the administration procedures (i.e., in the rat and shorter duration non-rodent studies).	The Xerava SmPC contains guidance on how to minimise the risk of infusion-site reactions by using an infusion time of approximately 1 hour. In case of serious reactions, eravacycline should be discontinued until a new intravenous access site is established. Additional measures to reduce the occurrence and severity of infusion site reactions include decreasing the eravacycline infusion rate and/or concentration.
Phototoxicity Eravacycline was negative for phototoxicity in an initial *in vitro* screening model utilising BALB/c 3T3 mouse fibroblasts. Eravacycline demonstrated phototoxic potential when the *in vitro* study was repeated using a current lot of eravacycline. In an *in vivo* study in pigmented rats repeat i.v. 40 mg/kg/day eravacycline resulted in no cutaneous or ophthalmologic clinical observations, nor any histopathological findings in the eyes of female Long Evans rats. These results confirmed that eravacycline was not phototoxic.	There is no evidence from the clinical development programme to suggest that eravacycline is phototoxic. However, photosensitivity is a recognised class effect of tetracyclines and therefore the Xerava SmPC contains guidance on possible adverse reactions that may occur during treatment with eravacycline as a tetracycline class antibiotic.
Haemolysis/Haemocompatibility Two non-GLP studies were conducted to evaluate the *in vitro* haemolytic potential of eravacycline in CD-1 mouse and human blood. The concentration of eravacycline required to produce a 10%, 50%, and 90% haemolysis in mouse or human blood was determined to be >5000 µM (equivalent to 2793 µg/mL), indicating i.v. compatibility.	Eravacycline did not cause significant haemolysis in human blood at any concentration tested, indicating i.v. compatibility at therapeutic plasma concentrations.
Immunotoxicity The effect of eravacycline on immune function was evaluated in the 13 week i.v. cynomolgus monkey toxicity study and a statistically significant decrease in anti-keyhole limpet haemocyanin (KLH) immunoglobulin G (IgG) antibody compared to the control group was observed in the 8 mg/kg/day males and females on Days 41, 43, 47, 53, and 57. The NOEL for immune function in the cynomolgus monkey was determined to be 4 mg/kg/day eravacycline. Other findings from 14-day i.v. toxicity studies were reported at 40 mg/kg/day in the Sprague Dawley rat, ≥12 mg/kg/day in the beagle dog, and 18 mg/kg/day in the cynomolgus monkey. These	In humans eravacycline is not expected to be immunotoxic. In patients with cIAI in the Phase 2/Phase 3 pool treated with eravacycline, there were inconsistent variations in haematology values throughout the course of study, with most values returning to normal ranges by the end of the study. Similar trends were observed for comparator-treated patients. There were no clear trends in shifts in any haematology parameters for eravacycline-treated subjects in the cIAI Only Phase 2/Phase 3 pool.

Key Safety findings (from non-clinical studies)	Relevance to human usage
findings included decreased WBC parameter indices that correlated with changes in spleen and/or thymus organ weights and the microscopic finding of bone marrow and/or lymphoid tissue atrophy.	
Inhibition of mitochondrial protein synthesis Eravacycline was evaluated for potential inhibition of mitochondrial DNA-encoded protein synthesis using the MitoBiogenesis™ kit, a HepG2 cell-based system using tetracycline and linezolid as comparators. The estimated IC_{50} values for inhibiting mitochondrial protein synthesis with eravacycline, tetracycline and linezolid were 1.4 µM, >10 µM, and 10 µM, respectively. Both cell growth and translation of the mtDNA-encoded COX enzyme were impacted by eravacycline. The estimated 50% inhibitory concentration (IC_{50}) values for inhibiting mitochondrial protein synthesis with eravacycline, tetracycline and linezolid were 1.4 µM, >10 µM, and 10 µM, respectively.	There is no evidence from the clinical development programme that eravacycline inhibits mitochondrial protein synthesis.

In conclusion the main toxicities observed in the non-clinical development programme were species specific histamine-like reactions and not applicable to humans. Important non-clinical safety findings include placental transfer of eravacycline to foetal blood and delayed skeletal ossification in the offspring in the rat and rabbit and eravacycline excretion in milk in the rat. The safety implications for humans are supported by the known class effects of tetracyclines that permanent teeth discolouration and a delay in ossification processes may occur in the infant following maternal exposure during the 2nd and 3rd trimester of pregnancy, exposure during lactation and in children under 8 years of age. Injection site findings were also observed at higher concentrations of eravacycline in the rat and shorter duration non-rodent studies when a catheter or vascular access port was not used.

The safety concerns for eravacycline from the non-clinical development programme include:

Important identified risk

- None

Important potential risk

- Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)

Part II: Module SIII - Clinical trial exposure

Eravacycline has been evaluated by i.v. and oral (p.o.) routes of administration in 26 completed clinical studies (Module 2.7.3, Summary of Clinical Efficacy and Module 2.7.4, Summary of Clinical Safety):

• 14 Phase 1 safety/pharmacokinetic studies in healthy subjects (i.v. or p.o. administration):

TP-34-P1-SAD-1, TP-434-P1-MAD-1, TP-434-004, TP-434-006, TP-434-Oral-P1-SAD-1, TP-434-002-P1-MAD-Oral, TP-434-003, TP-434-007, TP-434-009, TP-434-017, TP-434-022, TP-434-023, TP-434-027, TP-434-032

• 1 Phase 1 mass balance recovery study in healthy subjects (i.v. or p.o. administration):

TP-434-012

• 3 Phase 1 drug-drug interaction studies in healthy subjects (i.v. or p.o. administration):

TP-434-015, TP-434-016, TP-434-020

• 1 Phase 1 study in subjects with hepatic impairment (i.v. administration):

TP-434-013

• 1 Phase 1 study in subjects with renal impairment (i.v. administration):

TP-434-014

• 1 Phase 2 study in subjects with cIAI (i.v. administration):

TP-434-P2-cIAI-1

• 2 Phase 3 studies in subjects with cIAI (i.v. administration):

TP-434-008, TP-434-025

• 2 Phase 3 studies in subjects with cUTI (i.v. and p.o. administration):

TP-434-010, TP-434-021

• 1 Phase 1 study in paediatric subjects with suspected or confirmed bacterial infection (i.v. administration):

TP-434-028

• A total of 21 Phase 1 studies comprising 642 healthy subjects were undertaken.

There is one ongoing Phase 2 clinical study CS434-2023-001 to evaluate the safety and tolerability of intravenous eravacycline in children from 8 years to less than 18 years with complicated intra-abdominal infections (cIAI).

Exposure data from the following three studies in cIAI are presented below in Table 4 to Table 11:

- Study TP-434-P2-cIAI-1: Phase 2 study to assess the efficacy, safety and pharmacokinetics of 2 dose regimens of eravacycline (1.5 mg/kg i.v. q24h and 1.0 mg/kg i.v. q12h) compared with ertapenem (1.0 g i.v. q24h) in adult community-acquired cIAI
- Study TP-434-008: Pivotal Phase 3 study to assess the efficacy and safety of eravacycline (1.0 mg/kg i.v. q12h) compared with ertapenem (1.0 g i.v. q24h) in patients hospitalised for cIAI

- Study TP-434-025: Pivotal Phase 3 study to assess the efficacy, safety and pharmacokinetics of eravacycline (1.0 mg/kg i.v. q12h) compared with meropenem (1.0 g i.v. q8h) in patients hospitalised for cIAI

In these Phase 2 and Phase 3 studies, a total of 629 subjects with cIAI were treated with eravacycline, including 576 subjects treated with eravacycline 1.0 mg/kg q12h (the commercial dose) and 53 subjects treated with eravacycline 1.5 mg/kg q24h (547 subjects received comparator).

Exposure data from the following two studies in cUTI (which utilized i.v. and p.o. dosing) are presented below in Table 12 to Table 16:

- Study TP-434-010: Phase 3 study to assess the efficacy and safety of eravacycline (1.5 mg/kg i.v. q24h + 200 mg p.o. q12h) compared with levofloxacin (750 mg q24h + 750 mg p.o. q24h) in patients with cUTI
- Study TP-434-021: Phase 3 study to assess the efficacy and safety of eravacycline (1.5 mg/kg i.v. q24h for at least 5 days, then 750 mg levofloxacine p.o. q24h for up to 5 doses) compared with ertapenem (1.0 g i.v. q24h for at least 5 days, then 750 mg levofloxacine p.o. q24h for up to 5 doses) in patients with cUTI.

In these Phase 3 studies, a total of 1056 subjects with cUTI were treated with eravacycline, all received 1.5 mg/kg q24h (the commercial dose) including 455 who additionally received 200 mg p.o. q12h orally (1050 subjects received comparators). (Note: A lead-in phase for TP-434-010 including 48 subjects who received 1.5 mg/kg i.v. q24h + 200 mg p.o. q12h and 46 who received 1.5 mg/kg i.v. q24h + 250 mg p.o. q12h is not included in the respective tables below).

Table 4: SIII.1: Duration of exposure for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection		
Duration of exposure	Patients	Person days
< 4 days	15	34
4 – 7 days	353	2043
> 7 – 14 days	30	2288
> 14 days	14	210
Total	629	4575

Table 5: SIII.2: Age group and gender for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection				
Age group	Patients		Person days	
	M	F	M	F
< 18 years	0	0	0	0
18 – 64 years	280	177	1944	1284
≥ 65 years*	94	78	752	595
≥ 75 years*	30	29	247	229
Total	374	255	2696	1879

*Note: Data for the categories ≥ 65 years and ≥ 75 years are overlapping

Table 6: SIII.3: Dose for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection		
Dose of exposure	Patients	Person days
1.0 mg/kg q12h	576	4219
1.5 mg/kg q24h	53	356
Total	629	4575

Table 7: SIII.4: Racial group and ethnic origin for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection		
Racial group	Patients	Person days
Caucasian	585	4287
Black / African American	2	7
Asian	37	252
American Indian / Alaska Native	0	0
Native Hawaiian / Other Pacific Islander	0	0
Other	4	23
Missing	1	6
Total	629	4575
Ethnic origin	Patients	Person days
Hispanic or Latino	14	86
Non-Hispanic or Latino	607	4448
Missing	8	41
Total	629	4575

Table 8: SIII.5: Region for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection		
Region	Patients	Person days
Europe	567	4158
North America	26	170
Rest of world	36	247
Total	629	4575

Table 9: SIII.6: APACHE II score for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection		
APACHE II score	Patients	Person days
< 10	501	3541
≥ 10	126	1017
Missing	2	17
Total	629	4575

APACHE II: acute physiology and chronic health evaluation II

Table 10: SIII.7: Renal function for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection		
Renal function	Patients	Person days
Creatinine clearance < 15 mL/min	1	8
Creatinine clearance 15 to < 60 mL/min	49	401
Creatinine clearance ≥ 60 mL/min*	567	4088
Creatinine clearance ≥ 130 mL/min*	214	1522
Missing	12	78
Total	629	4575

* Note: Data for the categories creatinine clearance ≥ 60 mL/min and creatinine clearance ≥ 130 mL/min are overlapping

Table 11: SIII.8: Hepatic function for eravacycline treated patients with cIAI in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025

Complicated intra-abdominal infection		
Hepatic function	Patients	Person days
AST and ALT ≤ 2xULN	525	3813
AST and ALT > 2xULN	59	457
Missing	45	305
Total	629	4575
Child-Pugh class A	451	3143
Child-Pugh class B	89	748
Child-Pugh class C	0	0
Missing	89	684
Total	629	4575

AST: aspartate aminotransferase; ALT: alanine transaminase; ULN: upper limit of normal

Table 12: SIII.10: Duration of exposure for eravacycline treated patients with cUTI in TP-434-010 and TP-434-021

Complicated urinary tract infection		
Duration of exposure	Patients	Person days
< 4 days	27	53
4 – 7 days	636	4386
> 7 – 14 days	393	3910
Total	1056	8349

Table 13: SIII.11: Age group and gender for eravacycline treated patients with cUTI in TP-434-010 and TP-434-021

Complicated urinary tract infection				
Age group	Patients		Person days	
	M	F	M	F
< 18 years	0	0	0	0
18 – 64 years	202	427	1634	3224
≥ 65 years*	233	194	1951	1540
≥ 75 years*	73	83	596	645
Total	435	621	3585	4764

*Note: Data for the categories ≥ 65 years and ≥ 75 years are overlapping

Table 14: SIII.12: Dose for eravacycline treated patients with cUTI in TP-434-010 and TP-434-021

Complicated urinary tract infection		
Dose of exposure	Patients	Person days
1.5 mg/kg q24h IV	455	3093
1.5 mg/kg q24h IV plus 200 mg BID PO	601	5256
Total	1056	8349

Table 15: SIII.13: Racial group and ethnic origin for eravacycline treated patients with cUTI in TP-434-010 and TP-434-021

Complicated urinary tract infection		
Racial group	Patients	Person days
Caucasian	1032	8186
Black / African American	16	109
Asian	4	31
American Indian / Alaska Native	0	0
Native Hawaiian / Other Pacific Islander	0	0
Other	4	23
Missing	0	6
Total	1056	8349
Ethnic origin	Patients	Person days
Hispanic or Latino	25	179
Non-Hispanic or Latino	1031	8170
Missing	0	0
Total	1056	8349

Table 16: SIII.14: Region for eravacycline treated patients with cUTI in TP-434-010 and TP-434-021

Complicated urinary tract infection		
Region	Patients	Person days
Europe	1010	8041
North America	19	133
Rest of world	27	175
Total	1056	8349

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

The main exclusion criteria for Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025 are detailed below. Exclusion criteria applied to ensure standardisation of the trial population (rather than safety-related exclusion criteria) that are common to the majority of clinical studies are not presented, such as participation in any investigational drug or device study within 30 days prior to study, prior exposure to study treatment (eravacycline) in a clinical trial, and refusing medical care (mechanical ventilation, dialysis or hemofiltration, cardioversion or any other resuscitative measures and drug/fluid therapy) at the time of consent.

History of moderate or severe hypersensitivity reactions to tetracyclines or carbapenems or β-lactam antibiotics or to any of the excipients contained in the study drug formulations

Reason for exclusion: Patients who are hypersensitive to any component of the product should not receive eravacycline on grounds of safety. Including these patients may affect the safety and efficacy evaluation of eravacycline and put the patients at risk. Likewise, patients with hypersensitivity to carbapenems or β-lactam antibiotics were excluded for the same reasons in relation to carbapenems and β-lactam antibiotics.

Is it considered to be included as missing information?: No

Rationale: Hypersensitivity to the active substance, to any of the excipients or to tetracycline class antibiotics are contraindications in section 4.3 of the Xerava SmPC. Healthcare professionals are also warned that serious and occasionally fatal hypersensitivity reactions are possible and have been reported with other tetracycline class antibiotics. In case of hypersensitivity reactions, treatment with eravacycline must be discontinued immediately and appropriate emergency measures must be initiated. Hypersensitivity is listed as an adverse reaction of eravacycline with a frequency of uncommon (≥1/1,000 to <1/100). It is not expected that patients with hypersensitivity to eravacycline, its excipients or to tetracycline class antibiotics will be administered eravacycline. No such restriction is applied to patients with hypersensitivity to carbapenems or β-lactam antibiotics and there are no known or expected safety concerns for use of eravacycline in these patients.

Considered unlikely to survive the 6-8 week study period

- **Any rapidly-progressing disease or immediately life-threatening illness, including acute hepatic failure, respiratory failure and septic shock**
- **Requirement for vasopressors (prior to enrolment) at therapeutic dosages (i.e., dopamine >5 µg/kg/min, any dose of norepinephrine, epinephrine or phenylephrine) to maintain a systolic blood pressure ≥90 mm Hg or a mean arterial pressure ≥70 mm Hg following adequate fluid resuscitation**

Any other unstable or clinically significant concurrent medical condition (ie, class IV heart or lung disease, end stage renal disease, requiring haemodialysis, etc.) that would, in the opinion of the Investigator, jeopardise the safety of a subject, impact his or her expected survival through the end of the study participation, and/or impact his or her ability to comply with the protocol

Reason for exclusion: Excluding these patients standardises the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline.

Is it considered to be included as missing information?: No

Rationale: Patients with severe underlying conditions may benefit from eravacycline treatment.

No dose adjustments are considered necessary in patients with hepatic impairment.

Exposure may be increased in patients with severe hepatic impairment (Child-Pugh Class C). Therefore, such patients should be monitored for adverse reactions, particularly if these patients are obese and/or are also being treated with strong CYP3A inhibitors where the exposure may be further increased. In these cases, no recommendation on a posology can be made. There are no known or expected safety concerns for use of eravacycline in patients with hepatic impairment.

No dose adjustment is required in patients with renal impairment or in patients undergoing haemodialysis. Eravacycline may be administered without regard to the timing of haemodialysis. There are no known or expected safety concerns for use of eravacycline in patients with respiratory failure, septic shock or hypotension, class IV heart or lung disease, or patients with ESRD requiring haemodialysis.

Renal failure as defined as:

a. Threefold increase of serum creatinine to a known previous value, *OR*

b. Decrease in estimated glomerular filtration rate to <75% of a known previous value, *OR*

c. Urine output of <0.3 mL/kg per h for >24-h, *OR*

d. Anuria for >12-h, *OR*

e. Serum creatinine of >4 mg/dL (353.6 µmol/L) with an acute rise of 0.5 mg/dL (42.2 µmol/L) compared with a previous value, *OR*

f. Creatinine clearance <50 mL/min as estimated by the Cockcroft-Gault equation, *OR* $[mL/min] = \frac{(140-[yrs])\times Body\ Weight\ [kg] \times [0.85\ if\ Female]}{72\times Serum\ Creatinine\ [mg/dL]}$

g. Requires peritoneal dialysis, haemodialysis or haemofiltration

Reason for exclusion: Excluding these patients standardises the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline.

Is it considered to be included as missing information?: No

Rationale: Patients with renal failure may benefit from eravacycline treatment.
A pharmacokinetics (PK) study (Study TP-434-014) conducted in healthy subjects and patients with end-stage renal disease (ESRD) found that eravacycline was well tolerated by healthy subjects and patients with ESRD. There is no dose adjustment considered necessary in patients with renal impairment or in patients undergoing haemodialysis. There are no known or expected safety concerns for use of eravacycline in patients with renal impairment.

Presence or possible signs of significant hepatic disease:

a. Alanine aminotransferase or aspartate aminotransferase >3 x upper limit of normal (ULN); >5 x ULN for patients with hepatic abscess, *OR*

b. Total bilirubin >3 x ULN, unless isolated hyperbilirubinemia is directly related to the acute process, *OR*

c. Alkaline phosphatase >3 x ULN, *OR*

d. Subjects with diagnosis of hepatic failure

Reason for exclusion: Excluding these patients standardises the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline.

Is it considered to be included as missing information?: No

Rationale: Patients with significant hepatic disease may benefit from eravacycline treatment.
A PK study (Study TP-434-013) in healthy subjects and patients with hepatic impairment found that treatment with eravacycline was well tolerated by healthy subjects and subjects with mild,

moderate, and severe hepatic impairment. There are no dose adjustments necessary in patients with hepatic impairment, but as a precautionary measure patients with severe hepatic impairment (Child-Pugh Class C) should be monitored for adverse reactions, particularly if these patients are obese and/or are also being treated with strong CYP3A inhibitors where the exposure may be further increased. In these cases, no recommendation on a posology can be made. There are no known or expected safety concerns for use of eravacycline in patients with hepatic impairment.

Immunocompromised condition, including known human immunodeficiency virus (HIV) positivity (requiring anti-retroviral therapy or with CD4 count <300), acquired immune deficiency syndrome (AIDS), organ (bone marrow) transplant recipients, and hematological malignancy. Immunosuppressive therapy, including use of high-dose corticosteroids (e.g., >40 mg prednisone or equivalent per day for greater than 2 weeks)

Reason for exclusion: Immunocompromised patients are likely to be taking medications that could confound outcomes. Similarly, immunosuppressants and high-dose corticosteroids could modify the body's immune response. Excluding these patients standardises the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline.

Is it considered to be included as missing information?: No

Rationale: Patients who are immunocompromised are at risk of cIAI as these patients are vulnerable to opportunistic pathogens (Module SI). There are no known or expected safety concerns for use of eravacycline in this population.

Known or suspected current central nervous system (CNS) disorder that may predispose to seizures or lower seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy)

Reason for exclusion: Excluding these patients standardises the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline. The comparator in the study (ertapenem) is a carbapenem class antibiotic and use of a carbapenem antibiotic in these patients is contraindicated.

Is it considered to be included as missing information?: No

Rationale: There are no known or expected safety concerns for use of eravacycline in this population.

Antibiotic-related exclusions:

a. Receipt of effective antibacterial drug therapy for cIAI for a continuous duration of >24-h during the 72-h preceding enrollment (however, subjects with documented cIAI (ie, known baseline pathogen) who have received at least 72-h of antibiotic therapy and are considered treatment failures may be enrolled. Treatment failure is defined as persistent fever and/or clinical symptoms; or the development of a new intra-abdominal abscess after ≥72-h of antibiotic therapy), *OR*

b. Receipt of ertapenem or any other carbapenem, or tigecycline for the current infection *OR*

c. Need for concomitant systemic antimicrobial agents other than study drug

Reason for exclusion: Excluding these patients is a regulatory requirement and helps standardise the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline.

Is it considered to be included as missing information?: No

Rationale: In clinical practice it is anticipated that patients could be treated with a range of antibiotics up to the time at which eravacycline therapy is initiated. While attempts should be made not to overprescribe antibiotics because of the risk of antibiotic resistance (Module SI, Module SVII), the aim of effectively treating the patient may lead to use of multiple antibiotics in short succession if initial therapy is ineffective.

There are no known or expected safety concerns for use of eravacycline in this population.

Known or suspected inflammatory bowel disease or associated visceral abscess

Reason for exclusion: Excluding these patients standardises the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline.

Is it considered to be included as missing information?: No

Rationale: There are no known or expected safety concerns for use of eravacycline in patients with known or suspected inflammatory bowel disease or associated visceral abscess.

The anticipated need for systemic antibiotics for a duration of more than 14 days

Reason for exclusion: These patients were excluded to ensure the treatment of the patient was not compromised through their participation in the clinical trial and that the study design was adhered to as much as possible.

Is it considered to be included as missing information?: No

Rationale: The recommended dose regimen of Xerava is 1 mg/kg every 12 hours for 4 to 14 days as reflected in section 4.2 of the Xerava SmPC. In patients co-administered strong CYP3A4 inducers the recommended dose regimen is 1.5 mg/kg eravacycline every 12 hours for 4 to 14 days. There are no known or expected safety concerns for use of eravacycline in this population subsequent to prolonged exposure.

Systemic malignancy that required chemotherapy, immunotherapy, radiation therapy or antineoplastic therapy within the previous 3 months or which is anticipated to begin prior to the TOC visit

Reason for exclusion: Excluding patients with malignancies who may require other therapies at the time of the clinical trial standardises the study population as their inclusion may interfere with the evaluation of the efficacy and safety of eravacycline.

Is it considered to be included as missing information?: No

Rationale: Eravacycline has been assessed in multiple *in vitro* studies to evaluate the potential for other medicinal products to affect the PK of eravacycline and to evaluate the potential for eravacycline to affect the PK of other medicinal products. The eravacycline dose should be increased by approximately 50% (1.5 mg/kg IV q12h for 4 to 14 days) when co-administered with rifampicin or other strong CYP3A inducers and the Xerava SmPC recommends that patients receiving strong CYP3A inhibitors with a combination of factors that may increase the exposure, such as severe hepatic impairment and/or obesity should be monitored for adverse reactions. However, no dose adjustments are required nor specific guidance recommended for concomitant

administration of other medicinal products with eravacycline as detailed in Section 4.5 of the Xerava SmPC.

No safety concerns are expected or anticipated with concomitant administration of cancer therapies.

Known at study entry to have cIAI caused by a pathogen(s) resistant to one of the study drugs

Reason for exclusion: Including these patients would have potentially put them at unnecessary risk and interfered with the study efficacy results.

Is it considered to be included as missing information?: No

Rationale: In clinical practice patients known to be resistant to eravacycline would unlikely be treated with this antibiotic. The mechanism of resistance and the susceptibility testing breakpoints are presented in section 5.1 of the Xerava SmPC.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare (≥1/10,000 to <1/1,000) adverse reactions or adverse reactions with a long latency beyond 50 days which was the maximum duration of observation in the clinical development studies after the first dose of eravacycline.

Adverse reactions that are due to prolonged exposure are not expected as eravacycline should be limited to 4 to 14 days duration of treatment as detailed in section 4.2 of the Xerava SmPC.

Adverse reactions that are due to cumulative exposure are not applicable as there is no evidence that eravacycline accumulates or causes severe adverse reactions due to cumulative effects.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 17: SIV.3: Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with hepatic impairment (Child-Pugh Class B): 89 patients, 748 patient days in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025 (Table 11; Module SIII)

• Patients with renal impairment	Patients with renal impairment: CrCl 15 to < 60 mL/min 49 patients,401 patient days and CrCl < 15 mL/min 1 patient, 8 patient days in Phase 2 Study TP-434-P2-cIAI-1, Phase 3 Study TP-434-008 and Phase 3 Study TP-434-025 (Table 10; Module SIII)
• Patients with cardiovascular impairment	There were no exclusion criteria for patients with cardiovascular impairment (patients with congestive heart failure, atherosclerotic disease and myocardial ischemia were enrolled in the studies), with the exception of patients with class IV heart disease in Phase 3 Study TP-434-025.
• Immunocompromised patients	Immunocompromised patients were excluded from clinical trial participation (Section SIV.1). The Xerava SmPC advises that in clinical trials in cIAI there were no immunocompromised patients.
• Patients with a disease severity different from inclusion criteria in clinical trials	Phase 3 Study TP-434-008 had no restrictions on disease severity as assessed by the APACHE II score. The Xerava SmPC advises that in clinical trials in cIAI the majority of patients (80%) had APACHE II scores <10 at baseline.
Population with relevant different ethnic origin	Not included in the clinical development programme
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development programme Since eravacycline exposure is not dependent upon CYP enzymes or transporters, genetic variation in these patients will not affect exposure.
Other	Not included in the clinical development programme

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Eravacycline has been approved for the treatment of adults with cIAI in the USA, United Kingdom, EU, Iceland, Norway, Lichtenstein, China (Mainland, Hong Kong, Taiwan) and Singapore. The international birth date (IBD) is 27-Aug-2018.

SV.1.1 Method used to calculate exposure

- Post-authorisation exposure was calculated using a defined dosing regimen. The defined dosing regimen was calculated as follows:
- Defined dosing regimen calculation
- The patient was an adult weighing 70 kg who received Xerava 1 mg/kg (70 mg) twice daily for the treatment of cIAI.
- The patient was treated with Xerava for 7 days for a total treatment regimen of 980 mg
- Each vial of Xerava contains 50 mg
- Each dose of Xerava requires 2 vials for a total treatment regimen of 28 vials
- The total number of vials sold divided by the defined dosing regimen received yields the total number of patients exposed.

This calculation is halved for determining patient exposure based on the sales of 100 mg vials. A total treatment regimen with 100 mg vials is considered to be 14 vials.

SV.1.2 Exposure

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Eravacycline has been marketed in the USA since September 2018. It was placed on the market in the EU (Netherlands) in September 2021. The estimated cumulative post-authorisation exposure worldwide by the DLP of this RMP is 72,759 patients including 6,172 in Europe (EU and UK).

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

There have been no reports of abuse of eravacycline in the clinical development programme and there is no evidence of potential for abuse or misuse of eravacycline for illegal purposes. While no studies to assess the abuse potential of eravacycline have been conducted, eravacycline, like other antibiotics of its class, is not likely to be abused or produce dependence effects.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

- nausea
- vomiting
- diarrhoea

The most frequently reported gastrointestinal treatment-related adverse events (AEs), adverse drug reactions (ADRs), of eravacycline in the clinical development programme (eravacycline 1.0 mg/kg q12h i.v. cIAI Phase 2 and Phase 3 studies; N=576) were nausea (3.0%), vomiting (1.9%) and diarrhoea (0.7%). They were mainly mild or moderate in severity and with very few events leading to discontinuation of eravacycline. These are known adverse effects of the tetracycline class but are not expected to impact the benefit/risk of eravacycline in clinical practice administered for serious and potentially life-threatening cIAI.

Nausea, vomiting and diarrhoea are not classified as important risks of eravacycline based on the nature of the ADRs observed and that these are expected to be easily managed during the short term use of eravacycline (4 to 14 days duration of treatment) and only rarely led to discontinuation of study drug in the clinical studies.

2. Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Anaphylactic reaction

Anaphylactic reactions have not been observed with eravacycline in the clinical development programme for cIAI but it is recognised that life-threatening anaphylactic reactions may occur with all medications including eravacycline as a tetracycline antibiotic.

In the Phase 3 Study TP-434-008 hypersensitivity was reported by two patients treated with eravacycline but only one of the AEs was considered related to eravacycline. These isolated events described as ‘allergic reaction’ and ‘allergy symptoms’, coded to the Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) hypersensitivity, remained local to the puncture site and there was no reported urticaria, respiratory symptoms, changes in vital signs or other symptoms of anaphylaxis.

The Xerava SmPC advises that serious and occasionally fatal hypersensitivity reactions are possible and have been reported with other tetracycline class antibiotics and that in case of hypersensitivity reactions, treatment with eravacycline must be discontinued immediately and

appropriate emergency measures must be initiated. Hypersensitivity is listed as an adverse reaction of eravacycline with a frequency of uncommon (≥1/1,000 to <1/100).

There is currently insufficient evidence to justify the inclusion of anaphylactic reaction as an important risk of eravacycline.

- Infusion site reaction

An infusion site reaction is an expected ADR of eravacycline as an antibiotic administered intravenously and listed in the Xerava SmPC with a frequency of common (≥1/100 to <1/10).

In the clinical development programme infusion site reactions were found to be manageable, with all AEs classified as mild to moderate in severity and consistent with infusion site reactions seen with i.v. administration of other antibiotic treatments. A total of 39/576 eravacycline 1.0 mg/kg q12h IV treated subjects in the cIAI clinical studies (6.8%) experienced TEAEs in the Infusion Site Complication CMQ. Treatment-related infusion site reactions occurred in 30/576 subjects with cIAI treated with eravacycline (5.2%). The most frequently reported treatment-related TEAEs by PT included infusion site phlebitis, phlebitis and infusion site thrombosis. There were no serious or severe events in the Infusion Site Complications CMQ. Across the safety population, no subjects discontinued study drug due to events meeting the CMQ criteria.

Infusion site reactions in the clinical setting are expected to be manageable and should not have a significant impact on the patient or require hospitalisation but it is possible that severe infusion site reactions may occur. Infusion site reactions can be minimised through longer infusions and using lower concentrations. During the clinical development programme eravacycline infusion concentration and infusion duration adjustments led to a decrease in infusion site reaction ADRs from 9.2% (33/358) in the Phase 1 studies to 5.2% (30/576) in the cIAI Phase 2 and Phase 3 studies.

To minimise the risk of infusion-site reactions an infusion time of over approximately 1 hour is recommended in the Xerava SmPC and in case of serious reactions, eravacycline should be discontinued until a new intravenous access site is established. Additional measures to reduce the occurrence and severity of infusion site reactions include decreasing the eravacycline infusion rate and/or concentration.

Infusion site reactions are not considered an important risk of eravacycline as the risk has been quantified in the clinical studies and can be managed in clinical practice through adhering to the guidance in the Xerava SmPC.

- Hepatotoxicity

Drug induced liver injury has been reported in patients treated with other classes of broad spectrum antibiotics.

Eravacycline was not found to be hepatotoxic in the clinical development programme.

A total of 10/576 eravacycline 1.0 mg/kg q12h IV treated patients in the cIAI clinical studies (1.7%) experienced TEAEs meeting the Hepatic Disorders standardised MedDRA query (SMQ). Only 1 event, alanine aminotransferase (ALT) increased (0.2%), was considered treatment related, and there were three treatment-unrelated events (0.5%). Within the cIAI-only Phase 2/Phase 3 pool of subjects (n=576), there were three treatment-unrelated events of aspartate aminotransferase (AST) increased (0.5%). All three events were mild in severity, non-serious and the outcome was recovered/resolved with no change to the study medication. Within the

cIAI-only Phase 2/Phase 3 pool of subjects (n=576), there were no events of hyperbilirubinaemia but in the All Phase 2/Phase 3 pool of subjects which includes the cUTI study, and the cIAI subjects treated with eravacycline 1.5 mg/kg q24h, there was 1/1176 (<0.1%) treatment-emergent but treatment-unrelated event of blood bilirubin unconjugated increased. There were no cases of drug induced liver injury caused by eravacycline. Aspartate aminotransferase increased, alanine aminotransferase increased and hyperbilirubinaemia are listed as adverse reactions of eravacycline with frequencies of uncommon (≥1/1,000 to <1/100) in the Xerava SmPC.

There is currently insufficient evidence to justify the inclusion of hepatotoxicity as an important risk of eravacycline.

- Infections including cellulitis, fungal infection, and post-operative wound infection

Infections were observed with a low frequency in the clinical development programme. Infection ADRs observed in eravacycline treated patients in the cIAI Phase 2 and Phase 3 studies (N=576) occurred in 4 patients (0.7%) and comprised cellulitis (0.2%), fungal infection (0.2%), peritoneal abscess (0.2%) and post-operative wound infection (0.2%). None of these ADRs were serious.

Infections are not expected to impact the benefit/risk of eravacycline in clinical practice administered for serious and potentially life-threatening cIAI.

There is currently insufficient evidence to justify the inclusion of infections as an important risk of eravacycline.

- Overdose

No reports of overdose were reported in the clinical development programme. Intravenous administration of eravacycline at a single dose of 1.5 mg/kg every 24 hours or 1.0 mg/kg every 12 hours in healthy subjects has been adequately tolerated. The Xerava SmPC advises that in studies administering up to 3 mg/kg eravacycline to healthy subjects it has been observed that doses higher than the recommended dose lead to a higher rate of nausea and vomiting and that in the case of suspected overdose eravacycline should be discontinued and the patient monitored for adverse reactions.

There is currently insufficient evidence to justify the inclusion of overdose as an important risk of eravacycline.

- Medication errors

In the clinical development programme there were no medication error AEs reported.

There is currently insufficient evidence to justify the inclusion of medication errors as an important risk of eravacycline.

- Occupational exposure

A study nurse accidently splashed approximately 1 mL of unspecified reconstituted study drug (eravacycline 0.3 mg/mL, eravacycline 0.2 mg/mL, or ertapenem 16.7 mg/mL) into the conjunctiva of her eye during preparation of the i.v. study drug (Study TP-434-P2-cIAI-1). The nurse rinsed her eye with water for approximately five minutes but approximately two and a half hours later she started experiencing mild urticaria, itching, warmth, swelling of the eyelid, tachycardia, sternal oppression, and rash on her face and neck. After she administered methylprednisolone 40 mg her symptoms gradually subsided in the next few hours. The next morning, upon examination, the physician noted only the residual eyelid oedema; however, the

nurse complained of sternal oppression, which subsided over the next three days. All the allergic reaction symptoms resolved in three days with no residual long lasting effects.

The eravacycline product information, comprising the SmPC for healthcare professionals, the Package Leaflet (PL) for patients and the label, provides comprehensive guidance on the storage, reconstitution, indication and other measures to take in relation to the correct use of the medicinal product.

There is currently insufficient evidence to justify the inclusion of occupational exposure as an important risk of eravacycline.

- Off-label use

Eravacycline is intended for the treatment of cIAI in adults and adolescents from the age of 12 years weighing at least 50 kg.

During the clinical development programme eravacycline was evaluated in a Phase 3, randomised, double-blind, double-dummy, multicentre, prospective study to assess the efficacy and safety of eravacycline i.v. with transition to p.o. eravacycline compared with levofloxacin in the treatment of cUTI, including pyelonephritis (Study TP-434-010). The study was completed, but the primary endpoint was not met. There is also a Phase 3, randomised, double-blind, double-dummy, multicentre, prospective study assessing the efficacy and safety of i.v. eravacycline compared with ertapenem in cUTI (Study TP-434-021). It is possible that eravacycline could be used off-label for the treatment of cUTI or for other non-indicated infections but no safety concerns are expected in these populations.

There is currently insufficient evidence to justify the inclusion of off-label use as an important risk of eravacycline.

3. Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g. actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Drug interactions

Eravacycline has been assessed in multiple *in vitro* studies to evaluate the potential for other medicinal products to affect the PK of eravacycline and to evaluate the potential for eravacycline to affect the PK of other medicinal products. In most cases the changes were considered unlikely to be of clinical significance but in patients co-administered strong CYP3A4 inducers the recommended dose regimen is 1.5 mg/kg eravacycline every 12 hours for 4 to 14 days.

The Xerava SmPC also contains a warning relating to concomitant use of strong CYP3A4 inducers:

Concomitant use of strong CYP3A4 inducers
Medicines that induce CYP3A4 are expected to increase the rate and extent of metabolism of eravacycline. CYP3A4 inducers exert their effect in a time-dependent manner, and may take at least 2 weeks to reach maximal effect after introduction. Conversely, on discontinuation, CYP3A4 induction may take at least 2 weeks to decline. Co-administration of a strong CYP3A4 inducer (such as phenobarbital, rifampicin, carbamazepine, phenytoin, St. John's Wort) is expected to reduce the effect of eravacycline.

Guidance from Section 4.5 of the Xerava SmPC summarises the relevant drug interaction data:

Potential for other medicinal products to affect the pharmacokinetics of eravacycline
Concomitant administration of the strong CYP 3A4/3A5 inducer rifampicin altered the pharmacokinetics of eravacycline, decreasing exposure by approximately 32% and increasing clearance by approximately 54%. The eravacycline dose should be increased by approximately 50% (1.5 mg/kg IV q12h) when co-administered with rifampicin or other strong CYP3A inducers such as phenobarbital, carbamazepine, phenytoin and St. John's Wort.

Concomitant administration of the strong CYP3A inhibitor itraconazole altered the pharmacokinetics of eravacycline, increasing C_{max} by approximately 5% and AUC_{0-24} by approximately 23%, and decreasing clearance. The increased exposure is not likely to be clinically significant; thus, no dose adjustment is required when eravacycline is co-administered with CYP3A inhibitors. However, patients receiving strong CYP3A inhibitors (for example ritonavir, itraconazole, clarithromycin) with a combination of factors that may increase the exposure, such as severe hepatic impairment and/or obesity should be monitored for adverse reactions.

In vitro, eravacycline was shown to be a substrate for the transporters P-gp, OATP1B1 and OATP1B3. A drug-drug interaction in vivo cannot be excluded and co-administration of eravacycline and other medicinal products that inhibit these transporters (examples of OATP1B1/3 inhibitors; atazanavir, cyclosporine, lopinavir, and saquinavir) may increase the eravacycline plasma concentration.

Potential for eravacycline to affect the pharmacokinetics of other medicinal products
In vitro, eravacycline and its metabolites are not inhibitors or inducers of CYP enzymes or transport proteins. Interactions with medicinal products that are substrates for these enzymes or transporters are therefore unlikely.

There is currently insufficient evidence to justify the inclusion of drug interactions as an important risk of eravacycline.

- Pancreatitis

Pancreatitis is a class effect of tetracycline class antibiotics and therefore pancreatitis was identified as an AE of special interest in the clinical development programme. In the cIAI Phase 2 and Phase 3 studies (N=576) TEAEs in the Acute Pancreatitis SMQ were identified for 6 (0.1%) eravacycline-treated subjects, including pancreatic necrosis (1 subject), pancreatitis acute (2 subjects), pancreatitis necrotising (1 subject), lipase increased + nausea (2 subjects), and lipase increased + vomiting (1 subject).

None of these TEAEs were considered related to eravacycline. Thus, there were no acute pancreatitis ADRs. However as pancreatitis is a listed ADR in the SmPCs of tigecycline (Tygacil 50 mg powder for solution for infusion SmPC), tetracycline (Tetracycline Tablets BP 250 mg SmPC) and minocycline (Minocycline Tablets 100 mg SmPC) and TEAEs were observed with eravacycline, pancreatitis is listed as an ADR in section 4.8 of the Xerava SmPC with a frequency of uncommon (≥1/1,000 to <1/100) but not included as an important risk of eravacycline.

4. Known risks that do not impact the risk-benefit profile:

- Tetracycline class effects (photosensitivity, pseudotumor cerebri, and anti-anabolic action which have led to increased BUN, azotaemia, acidosis, and hyperphosphataemia)

Tetracycline class adverse reactions that have not been observed with eravacycline but are listed in the Xerava SmPC as tetracycline class effects include photosensitivity, *pseudotumor cerebri*, and anti-anabolic action which have led to increased BUN, azotaemia, acidosis, and hyperphosphataemia.

These are known adverse effects of the tetracycline class and therefore potential risks of eravacycline but they are not expected to impact the benefit/risk of eravacycline in clinical practice administered for serious and potentially life-threatening cIAI.

There is currently insufficient evidence to justify the inclusion of these tetracycline class effects as important potential risks of eravacycline.

5. Other reasons for considering the risks not important:

- Transmission of infectious agents

None of the excipients used in the manufacturing process for eravacycline powder for concentrate for solution for infusion are derived from human or animal origin.

There is currently insufficient evidence to justify the inclusion of transmission of infectious agents as an important risk of eravacycline.

- Potential for misuse for illegal purposes

As detailed in Module SVI, there is no evidence of potential for abuse or misuse of eravacycline for illegal purposes.

There is currently insufficient evidence to justify the inclusion of potential for misuse for illegal purposes as an important risk of eravacycline.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risk:

None

Important Potential Risk 1: Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)

Eravacycline, like other tetracycline class antibiotics, may induce permanent dental defects (discolouration and enamel defects) and a delay in ossification processes in the foetus exposed *in utero* during the 2nd and 3rd trimester, through exposure during lactation and in children less than 8 years of age due to accumulation in tissues with a high calcium turnover and formation of calcium chelate complexes.

Animal studies indicate that eravacycline crosses the placenta and is found in foetal plasma and that delayed skeletal ossification was observed in the offspring in the rat and rabbit (Module SII). No pregnancies were observed among eravacycline-treated patients in the cIAI clinical studies. However there were 2 cases of eravacycline exposure during pregnancy in Phase 3 Study TP-434-010 in which eravacycline was evaluated for the treatment of cUTI, including one pregnancy that was electively terminated and another pregnancy which resulted in a healthy child. In clinical practice eravacycline may be used during the 2nd and 3rd trimester of pregnancy if there are no alternative antibiotics available to treat the cIAI as a result of increased resistance to existing therapies.

There was no exposure during lactation in the clinical development programme and therefore no permanent teeth discolouration or delay in ossification processes in the infant was observed. It is unknown whether eravacycline and its metabolites are excreted in human breast milk but animal studies have shown excretion of eravacycline and its metabolites in milk in the rat (Module SII). In clinical practice eravacycline may be used during lactation if the benefit of breast-feeding for the child and the benefit of therapy for the woman is considered to outweigh the risks of continuing therapy and discontinuing breast-feeding as outlined in the Xerava SmPC.

. The safety and efficacy of Xerava in children less than 12 years of age or adolescents with body weight below 50 kg have not been established. The dosing regimen for adolescents (12 years and older, weighing at least 50 kg) is based on pharmacokinetic modelling and simulations, and data from the Phase 1 pediatric trial (TP-434-028). As a tetracycline class antibiotic eravacycline should not be used in children below 8 years of age as eravacycline has the potential for the same effects on teeth.

Risk-benefit impact:

Eravacycline use during the 2nd or 3rd trimester of pregnancy could result in teeth discolouration and a delay in ossification processes in the exposed foetus (Section SVII.3). The impact on the foetus is serious as permanent adverse effects on the teeth may occur. Similarly, eravacycline exposure to the breast-fed infant and in children under 8 years of age can also induce permanent teeth discolouration.

While use of eravacycline in these patient populations is not expected to be substantial, it is also recognised that eravacycline has some important benefits over other antibiotics and therefore may be used despite the known risks in these populations. Eravacycline is highly active against clinically important MDR Gram-negative and Gram-positive aerobic and anaerobic pathogens, including Enterobacteriaceae that produce ESBLs and/or carbapenemases from all of the Ambler classes. Eravacycline also possesses potent activity against CRAB, including those with blaOXA carbapenemases and isolates displaying MDR (Sutcliffe et al., 2013).

Exposure during the 1st trimester of pregnancy, when pregnancy may not be realised, does not carry the same risk as tetracyclines are incorporated into the teeth and bones as the result of chelation with calcium ions in the molecular structure which only occurs during the period of the calcification process from 4 months *in utero* (Conchie et al., 1970). Accidental exposure is not anticipated as the patient and the healthcare professional should be aware of the pregnancy before eravacycline administration in the 2nd or 3rd trimester.

The recommended dose regimen of eravacycline is 1.0 mg/kg every 12 hours for 4 to 14 days (for patients co-administered strong CYP3A4 inhibitors the recommended dose is 1.5 mg/kg eravacycline every 12 hours for 4 to 14 days) and continuous breastfeeding multiple times a day would expose the breast-feeding infant to eravacycline at a critical period for teeth and bone

development. Similarly exposure in children under 8 years of age could result in permanent effects. While the risk of permanent teeth discolouration and a delay in ossification processes is theoretical and based on the recognised class effect of tetracyclines, the impact on the foetus, breast-fed infant and child could be substantial if permanent effects on the teeth and bones occur.

'Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)' is considered an important potential risk based on its permanent adverse effects on the foetus, infant and child.

Important Potential Risk 2: Pseudomembranous colitis

Pseudomembranous colitis is caused by toxigenic *Clostridioides difficile (C. difficile)*. *C. difficile*-associated diarrhoea has been reported with the use of nearly all antibacterial agents including the tetracyclines (Treloar et al., 1987) and may range in severity from mild diarrhoea to fatal colitis. In Phase 3 Study TP-434-025 there was one eravacycline-treated subject (0.1%) who developed *C. difficile* colitis 10 days after the last dose of eravacycline and after receiving other broad-spectrum antibiotics, which was non-serious, mild in severity, resolved and not related to study drug. Thus, no pseudomembranous colitis (*C. difficile*-associated diarrhoea) ADRs were observed in patients treated with eravacycline in the clinical development programme (Module 2.7.4, Summary of Clinical Safety).

Risk-benefit impact: Initial signs and symptoms of pseudomembranous colitis include diarrhoea, abdominal pain, fever, pus or mucus in stools, nausea and dehydration with possible complications of hypokalaemia, hypotension, renal failure, perforated or ruptured colon which may be life-threatening (Section SVII.3).

Pseudomembranous colitis, should it occur, is a serious condition but cIAI if not effectively treated can have life-threatening consequences (Module SI). The benefit of eravacycline as an effective treatment of cIAI outweighs any potential risk of pseudomembranous colitis that has yet to be confirmed as an ADR of eravacycline.

Pseudomembranous colitis is considered an important potential risk of eravacycline.

Important Potential Risk 3: Emergence of resistance

Antimicrobial resistance occurs naturally over time, usually through genetic changes but the misuse and overuse of antimicrobials in both humans and animals accelerates this process (WHO 2016). The appropriate use of antimicrobials is essential for reducing and preventing antimicrobial resistance.

Risk-benefit impact: As a novel, synthetic, broad-spectrum fluorocycline antibiotic, eravacycline is not expected to carry the same resistance as other widely used antibiotics. The C-7 and C-9 substitutions in eravacycline are not present in any naturally occurring or semisynthetic tetracyclines and the substitution pattern imparts microbiological activities including retention of *in vitro* potency against Gram-positive and Gram-negative strains expressing tetracycline-specific resistance mechanism(s) (i.e., efflux mediated by tet(A), tet(B), and tet(K); ribosomal protection as encoded by tet(M) and tet(Q). Eravacycline is not a substrate for the MepA pump in *Staphylococcus aureus* that has been described as a resistance mechanism for tigecycline. Eravacycline is also not affected by aminoglycoside inactivating or modifying enzymes.

The potential mechanisms of resistance to eravacycline are outlined in the Xerava SmPC. Resistance to eravacycline has been observed in *Enterococcus* harbouring mutations in rpsJ. There is no target-based cross-resistance between eravacycline and other classes of antibiotics such as quinolones, penicillins, cephalosporins, and carbapenems. Other bacterial resistance mechanisms that could potentially affect eravacycline are associated with upregulated, non-specific intrinsic multidrug-resistant (MDR) efflux.

Eravacycline is highly active against clinically important MDR Gram-negative and Gram-positive aerobic and anaerobic pathogens, including Enterobacteriaceae that produce ESBLs and/or carbapenemases from all of the Ambler classes. Eravacycline is also unique among antimicrobials in late-stage development in that it possesses potent activity against CRAB, including those with blaOXA carbapenemases and isolates displaying MDR (Sutcliffe et al., 2013).

However, it is recognised that microorganisms evolve and that poor infection control, inadequate sanitary conditions and inappropriate food-handling can encourage the spread of antimicrobial resistance (WHO 2016). To manage antimicrobial resistance, surveillance for resistance patterns to various antimicrobials is required.

Emergence of resistance is considered an important potential risk of eravacycline.

Missing information:

None

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable.

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

Important Identified Risk: None

Important Potential Risk: ***Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)***

Potential mechanisms:

The mechanism whereby tetracyclines are incorporated into the teeth and bones appears to be the result of chelation of the tetracycline with calcium ions in the molecular structure which only occurs during the period of the calcification process (Conchie et al., 1970). Such an effect on the teeth occurs during the last trimester of pregnancy and in early childhood.

Systemic administration of tetracyclines during development is associated with deposition of tetracycline within bone and the dental hard tissues where it has the ability to form complexes with calcium ions on the surface of hydroxyl apatite crystals (Watts and Addy 2001). Tetracycline is able to cross the placental barrier and should be avoided from 29 weeks *in utero*

until full term to prevent incorporation into the dental tissues. Since the permanent teeth continue to develop in the infant and young child, tetracycline administration should be avoided in children below the age of 8 years and in breast-feeding and expectant mothers (Watts and Addy 2001; Xerava SmPC). Specifically the most critical time to avoid the administration of tetracycline for the deciduous dentition is 4 months *in utero* to 5 months post-partum, with regard to the incisor and canine teeth. In the permanent dentition, for the incisor and canine teeth, this period is from 4 months post-partum to approximately 7 years of age.

In terms of effects on bone, when the tetracyclines are absorbed, they will incorporate into mineralising bone and can be detected by their fluorescence (Pautke et al., 2010). Additional biological effects of tetracyclines on bone formation have been reported, in the form of direct effects on the activities of bone-forming osteoblasts and osteoclasts, as low levels (less than 50 mg/ml) may induce osteogenesis, while high levels (more than 50 mg/ml) may inhibit this process, indicating a dose-related effect of tetracyclines on osteoblasts (Cheng et al., 2012). Tetracyclines can affect parameters of osteoclast function, inhibiting bone resorption through a number of pathways, including: (1) altering intracellular calcium concentration and interaction with the putative calcium receptor; (2) decreasing the ruffled border area and acid production; (3) diminishing lysosomal cysteine proteinase (cathepsin) secretion; (4) inducing cell retraction by affecting podosomes; (5) inhibiting osteoclast gelatinase activity; (6) selectively inhibiting osteoclast ontogeny or development; and (7) inducing apoptosis or programmed cell death of osteoclasts (Cheng et al., 2012).

Animal studies showed delayed skeletal ossification in the offspring in the rat and rabbit, evidence of placental transfer of eravacycline to foetal blood, and that eravacycline is excreted in milk in the rat (Module SII).

Evidence source(s) and strength of evidence:

Permanent teeth discolouration and a delay in ossification processes may occur in the foetus, breast-fed infant and child following maternal eravacycline treatment during the 2nd or 3rd trimester of pregnancy, through exposure to eravacycline through breast milk and in children under the age of 8 years, the time when the teeth and the bones are developing. These effects have not been observed with eravacycline in clinical studies but are known to occur with other tetracycline antibiotics through published studies in the medical literature (Watts and Addy 2001; Cheng et al., 2012; Conchie et al., 1970), and therefore are expected to occur with eravacycline. Animal studies have shown that eravacycline can cross the placenta similarly to other tetracycline antibiotics, can cause a delay in ossification in the offspring of exposed animals and that eravacycline is excreted in breast milk.

Characterisation of the risk:

No pregnancies were observed among eravacycline-treated patients in the cIAI studies and therefore there were no reports of permanent teeth discolouration or a delay in ossification processes in the foetus. However there have been 2 cases of eravacycline exposure during pregnancy in Phase 3 Study TP-434-010 in which eravacycline was evaluated for the treatment of cUTI, including one pregnancy that was electively terminated and another pregnancy which resulted in a healthy child.

There was no exposure during lactation or in children in the clinical development programme and therefore no reports of permanent teeth discolouration or a delay in ossification processes in the breast-fed infant or child under the age of 8 years.

As for other tetracycline class antibiotics, eravacycline may induce permanent dental defects (discolouration and enamel defects) and a delay in ossification processes in foetuses, exposed *in utero* during the 2nd and 3rd trimester, in infants exposed through lactation and in children under eight years of age due to accumulation in tissues with a high calcium turnover and formation of calcium chelate complexes.

For tetracyclines the colour changes involved depend upon the precise medication used, the dose and the period of time over which the medication was given. Teeth affected by tetracycline have a yellowish or brown-grey appearance which is worse on eruption and diminishes with time, and with exposure to light, changes the colour to brown, with the anterior teeth being particularly susceptible to light induced colour changes (Watts and Addy 2001). The same effect may be observed with eravacycline.

Risk factors and risk groups:

Infants whose mothers were taking eravacycline during the 2nd or 3rd trimester of pregnancy or who breast-feed from mothers taking eravacycline are at risk of permanent teeth discolouration and a delay in ossification processes. Children under the age of 8 years who take eravacycline are also at increased risk of these permanent effects.

Preventability:

The risk can be minimised through avoiding eravacycline exposure during the 2nd and 3rd trimester of pregnancy, avoiding eravacycline exposure during lactation and use in children under 8 years of age.

It is unknown whether eravacycline is excreted in human breast milk but animal studies have shown excretion of eravacycline in breast milk (Module SII). The Xerava SmPC highlights that long-term use of other tetracyclines during breast-feeding may result in significant absorption by the breast-fed infant, and is not recommended, because of the risk of dental discolouration and delay in ossification processes of the breast-fed infant. The SmPC advises that a decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Xerava should be made, taking into account the benefit of breast-feeding for the child, and the benefit of therapy for the woman.

The Xerava SmPC highlights that safety and efficacy of eravacycline in children less than 12 years of age or adolescent with body weight below 50 kg have not been established and that there are limited data on the use of eravacycline in pregnant women. While the potential risk for humans is unknown, eravacycline, as a tetracycline class antibiotic, may induce permanent dental defects (discolouration and enamel defects) and a delay in ossification processes in foetuses, exposed *in utero* during the 2nd and 3rd trimester, and in children under 8 years of age due to accumulation in tissues with a high calcium turnover and formation of calcium chelate complexes. Therefore, Xerava should not be used during pregnancy unless the clinical condition of the woman requires treatment with eravacycline.

Impact on the risk-benefit balance of the product:

The extent of exposure during the 2nd or 3rd trimester of pregnancy, during lactation and in children under 8 years of age is likely to be minimal if healthcare professionals are aware of the risks to the foetus, infant and child. However, the impact on the foetus, infant and child can be substantial as permanent effects on the teeth and bones may occur. In clinical practice eravacycline may be used during pregnancy if the clinical condition of the woman requires

treatment with eravacycline as outlined in the Xerava SmPC. Similarly eravacycline may be used during lactation if the benefit of breast-feeding for the child and the benefit of therapy for the woman is considered to outweigh the risks of continuing therapy and discontinuing breast-feeding as outlined in the Xerava SmPC.

Further characterisation of the risk in humans will be limited due to the expected limited exposure during pregnancy, lactation and in children under 8 years of age. A specific follow-up form will be used to seek further details of any initial ADR reports of tooth discolouration (Section III.1; Annex 4). Any new information is not expected to have a major impact on the risk-benefit balance of eravacycline.

Public health impact:

The overall public health impact is expected to be negligible as exposure of eravacycline during the 2nd or 3rd trimester of pregnancy, during lactation or in children under the age of 8 years is likely to be minimal given that it is a well-recognised risk with the tetracycline class of antibiotics and healthcare professionals should already be aware of the guidance to avoid exposure if possible.

Important Potential Risk: *Pseudomembranous colitis*

Potential mechanisms:

Pseudomembranous colitis is caused by toxigenic *C. difficile*. *C. difficile* is an obligate anaerobic organism and toxin-producing Gram-positive rod with the ability to form spores. Systemic administration of broad-spectrum antibiotics disrupts the normal colonic flora with subsequent *C. difficile* colonisation (Farooq et al., 2015). Following initial colonisation, clinically significant infection is mediated by toxin production.

The pathogenicity of *C. difficile* is mainly mediated by two exotoxins: toxin A (TcdA) and toxin B (TcdB) with the expression of TcdA and TcdB dependent upon environmental conditions and global regulators, including the availability of specific nutrients, temperature changes, and alteration of the redox potential (Di Bella et al., 2016). These toxins primarily disrupt the cytoskeletal structure and the tight junctions of target cells causing cell rounding and ultimately cell death. The tight junctions between neighbouring colonic cells allow infiltration by neutrophils and cause an inflammatory response characteristic of colitis (Farooq et al., 2015). Pseudomembranes form via this influx of neutrophils into the mucosa and further activation of the native immune system by the toxins. Activation of macrophages and monocytes causes the release of pro-inflammatory cytokines like interleukin (IL)-1, IL-8, tumour necrosis factor (TNF), and leukotriene B4, which lead to additional mucosal injury and focal microabscess and pseudomembrane formation (Farooq et al., 2015). Detectable *C. difficile* toxaemia is strongly associated with fulminant disease (Di Bella et al., 2016).

In vitro eravacycline demonstrates potent activity against *C. difficile*, making overgrowth less likely.

Evidence source(s) and strength of evidence:

Pseudomembranous colitis (*Clostridioides difficile*-associated diarrhoea) was not observed in patients treated with eravacycline in the clinical studies. However pseudomembranous colitis has been reported with nearly all antibacterial agents including the tetracyclines (Treloar et al., 1987)

and therefore may occur in a small number of patients treated with eravacycline in clinical practice.

Characterisation of the risk:

No pseudomembranous colitis (*C. difficile*-associated diarrhoea) ADRs were observed in patients with cIAI treated with eravacycline in the clinical development programme. In Phase 3 Study TP-434-025 there was one eravacycline-treated subject (0.1%) who developed *C. difficile* colitis 10 days after the last dose of eravacycline and after receiving other broad-spectrum antibiotics, which was non-serious, mild in severity, resolved and not related to study drug.

Nearly all antibacterial agents including the tetracyclines have been associated with *C. difficile*-associated diarrhoea (Treloar et al., 1987) and this may range in severity from mild diarrhoea to fatal colitis. Exposure to antibacterial agents can alter the normal flora of the colon leading to overgrowth of *C. difficile*. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. In rare cases, *C. difficile*-associated diarrhoea can be fatal.

Risk factors and risk groups:

Risk factors for pseudomembranous colitis include taking antibiotics, hospitalisation or residing in a nursing home, increasing age (especially over 65 years), a weakened immune system, a colon disease, such as inflammatory bowel disease or colorectal cancer, undergoing intestinal surgery and receiving chemotherapy treatment for cancer (Mayo Clinic 2017).

Preventability:

Prevention is through limiting antibiotic use. Hand washing and room cleaning in hospital can reduce the risk of transmission by the faecal oral route.

The risk to patients can be minimised by increasing healthcare professional and patient awareness of the risk of pseudomembranous colitis that is associated with the use of nearly all antibiotics and may range in severity from mild to life-threatening. The Xerava SmPC recommends that in cases where diarrhoea occurs during or subsequent to treatment with eravacycline, pseudomembranous colitis should be suspected and the use of supportive measures together with the administration of specific treatment for *C. difficile* considered. Medicinal products that inhibit peristalsis should not be given.

Impact on the risk-benefit balance of the product:

Initial signs and symptoms of pseudomembranous colitis may include diarrhoea that can be watery or even bloody, abdominal cramps, pain or tenderness, fever, pus or mucus in stools, nausea and dehydration. Symptoms of pseudomembranous colitis can commence as soon as one to two days after antibiotic administration, or as long as several weeks after completing the antibiotic treatment. *C. difficile* normally produces an acute infection which resolves with effective therapy typically within 2 weeks, though prolonged symptoms or recurrent infections are possible.

Pseudomembranous colitis can be life-threatening and possible complications include hypokalaemia, dehydration leading to hypotension, kidney failure, perforated colon, which can lead to an abdominal cavity infection, and toxic megacolon which could cause colon rupture (Mayo Clinic 2017).

Pseudomembranous colitis, should this occur in the clinical setting with eravacycline, may have a significant impact on the patient and require hospitalisation in serious cases.

The risk was further characterised through quantification of pseudomembranous colitis in Phase 3 cUTI Study TP-434-021 as a routine pharmacovigilance activity (Section III.1). There were no reported events of pseudomembranous colitis in the TP-434-021 study.

Public health impact:

Clostridioides difficile infection is the major identifiable cause of antibiotic-associated diarrhoea, responsible for 15 to 30% of all cases, and the primary cause of antibiotic-associated colitis (DePestel et al., 2013; Cohen et al., 2010). In a large European study evaluating *C. difficile* infection in 106 laboratories in 34 European countries the incidence of *C. difficile* infection varied across hospitals (weighted mean 4.1 per 10,000 patient-days per hospital, range 0.0-36.3) (Bauer et al., 2011). Detailed information was obtained for 509 patients and for 389 of these patients, isolates were available for characterisation. At follow-up, 101 (22%) of 455 patients had died, and *C. difficile* infection played a part in 40 (40%) of those deaths.

While the consequences of pseudomembranous colitis can have a serious outcome requiring treatment and hospitalisation, the frequency is expected to be low as pseudomembranous colitis was not observed with eravacycline treatment in the clinical development programme. The overall public health impact is therefore expected to be low.

Important Potential Risk: *Emergence of resistance*

Potential mechanisms:

The most important clinical mechanisms of resistance to tetracyclines result from acquisition of genetically mobile tetracycline resistance (*tet*) genes, which encode proteins that confer efflux of tetracyclines, or ribosomal protection (Chopra 2001; Chopra and Roberts 2001). In other cases resistance has arisen by point mutation in ribosomal RNA (e.g. in propionibacteria) (Chopra and Roberts 2001; Ross et al., 1998) or through the activity of innate (endogenous) bacterial efflux proteins that confer resistance to a number of structurally unrelated biocides and antibiotics as well as tetracyclines (Chopra and Roberts 2001).

Eravacycline was designed to overcome the two major acquired tetracycline-specific resistance mechanisms: ribosomal protection where a protein (e.g., tet[M]) mediates the removal of tetracycline from its binding site on the small ribosomal subunit and drug efflux (i.e., tet[A] and tet [K]) (Chopra 2001; Roberts 2005). As a fluorocycline, eravacycline is impervious to either mechanism, with equivalent microbiological activity against *E. coli* strains expressing either resistance determinant. Further, eravacycline showed potent mechanism-based activity in a coupled transcription/translation assay with or without the addition of tet(M), a widespread ribosomal protection protein. Thus, eravacycline should be active where legacy tetracyclines such as doxycycline, minocycline, and tetracycline are not. Eravacycline is not impacted by ESBLs, AmpC β-lactamases, and carbapenemases, including KPC, OXA, VIM and NDM-1, or other resistance mechanisms specific to other antibiotic classes.

Evidence source(s) and strength of evidence:

Antimicrobial resistance is one of the most serious global public health threats in this century (Prestinaci et al., 2015). The appropriate use of antibiotics is essential for reducing and preventing antimicrobial resistance. As a novel, synthetic, broad-spectrum fluorocycline

antibiotic, eravacycline is not expected to carry the same resistance as other widely used antibiotics, but as this may change, resistance levels need to be monitored through surveillance for resistance patterns.

Characterisation of the risk:

There was little evidence of resistance with eravacycline in the clinical development programme.

The emergence of resistance to eravacycline was evaluated during serial passage. There was no significant increase in eravacycline minimum inhibitory concentration (MIC) for the Gram-positive organisms *Staphylococcus aureus*, *Enterococcus faecalis*, or *Streptococcus pyogenes* during passage. Increases in eravacycline MIC were observed during 20 passages of E. coli (16-fold) and K. pneumoniae (32-fold). For *B. fragilis*, eravacycline MIC values increased during serial passage but these increases were not confirmed by broth microdilution MIC testing, indicating no true emergence of resistance for eravacycline and *B. fragilis*.

There was little evidence of cross-resistance to the majority of evaluated agents from other antibiotic classes with laboratory-derived eravacycline mutants with a few exceptions. Among eravacycline-selected Gram-negative mutants there was some evidence of cross-resistance to ciprofloxacin (*K. pneumoniae* and *A. baumannii*), and gentamicin (*A. baumannii*). As expected, eravacycline-selected mutants had reduced susceptibility to tigecycline demonstrating the potential for cross-resistance between these two agents.

Genetic characterisation data of laboratory-derived eravacycline mutants revealed that the likely mechanism of resistance among Gram-positive organisms was mutation of *rpsJ* resulting in alteration 30S ribosomal protein S10 near the tetracycline ribosomal binding site. For *K. pneumoniae*, mutations in either *lon* or *ramR*, both of which impact the expression of the MDR response, were identified within eravacycline-selected spontaneous and serial passage mutants. For *A. baumannii*, eravacycline-selected mutants with the highest eravacycline and tigecycline MIC values had a mutation in *adeS*, a gene involved in the regulation of the AdeABC multidrug efflux pump. For *E. coli* eravacycline-selected serial passage mutants, mutations in *lon* and *marR*, both presumably affecting expression of the MDR response, were identified.

The genetic characterisation data of laboratory-derived mutants combined with the data on eravacycline activity against isolates with characterised tetracycline-resistance indicate that:

- eravacycline retains activity against tetracycline-specific resistance mechanisms (RPP and efflux);
- like members of many other classes of antibiotics, eravacycline activity is negatively affected by expression of some MDR efflux pumps;
- eravacycline MIC values increase in the presence of target based mutations in 16S rRNA;
- reduced susceptibility to eravacycline is also associated with mutations encoding amino acid changes in 30S ribosomal protein S10 near the tetracycline ribosomal binding site.

Risk factors and risk groups:

Antimicrobial resistance occurs naturally over time, usually through genetic changes and the misuse and overuse of antimicrobials in both humans and animals accelerates this process (WHO 2016). Poor infection control, inadequate sanitary conditions and inappropriate food-handling can encourage the spread of antimicrobial resistance (WHO 2016). Factors that may affect the development of antimicrobial resistance include dose, duration of treatment and class of

antibiotic, disease transmission and exposure rates, host susceptibility (e.g., vaccination status), and transmissibility of the pathogen (Friedman and Whitney 2008).

Preventability:

Three areas have been the main foci for the prevention and control of antimicrobial resistance: (1) vaccines to reduce the burden of disease, (2) development of new antibiotics, and (3) reducing inappropriate antimicrobial use (Friedman and Whitney 2008).

The WHO is working closely with the Food and Agriculture Organization of the United Nations (FAO) and the World Organisation for Animal Health (OIE) in a 'One Health' approach to promote best practices to avoid the emergence and spread of antibacterial resistance, including optimal use of antibiotics in both humans and animals (WHO 2016). A global action plan on microbial resistance was initiated in May 2015 by the World Health Assembly (WHO 2015) with the following five strategic objectives:

- to improve awareness and understanding of antimicrobial resistance through effective communication, education and training;
- to strengthen the knowledge and evidence base through surveillance and research;
- to reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures;
- to optimise the use of antimicrobial medicines in human and animal health;
- to develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Antimicrobial surveillance schemes, such as the one run by the European Centre for Disease Prevention and Control (ECDC), focus on resistance levels to the various antimicrobials and outcomes on morbidity and mortality (Module SI).

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) provides clinical MIC breakpoints on wildtype and resistant microorganisms to advise on patient therapy (EUCAST 2017). Data on current MIC breakpoints, susceptibility and the list of species are provided in the Xerava SmPC.

Impact on the risk-benefit balance of the product:

Infections caused by resistant bacteria lead to up to two-fold higher rates of adverse outcomes compared with similar infections caused by susceptible strains (Friedman et al., 2016). These adverse outcomes may be clinical or economic and reflect primarily the failure or delay of antibiotic treatment. The magnitude of these adverse outcomes will be more pronounced as disease severity, strain virulence, or host vulnerability increases. The negative impacts of antibacterial resistance can be measured at the patient level by increased morbidity and mortality.

Resistance can lead to treatment failure, prolonged hospitalisation and death. For example there is an association between the development of antimicrobial resistance in *S. aureus*, enterococci, and Gram-negative bacilli and increases in mortality, morbidity, length of hospitalisation, and cost of healthcare (Cosgrove 2006). For many patients, inadequate or delayed therapy and severe underlying disease are primarily responsible for the adverse outcomes of infections caused by antimicrobial-resistant organisms. Patients infected with a resistant pathogen may experience

decreased effectiveness, increased toxicity, improper dosing of antimicrobial agents available for treatment, a delay in treatment with or the absence of microbiologically effective antimicrobials, and an increased need for surgery and other procedures as a result of these infections (Cosgrove 2006).

The risk will be further characterised through a 5-year observational study to monitor resistance of pathogens to eravacycline. The surveillance is being conducted in Europe, US and Asia/Pacific regions as an additional pharmacovigilance activity (Section III.2). The further characterisation is not expected to impact the risk-benefit balance of eravacycline.

Public health impact:

The estimated public health impact of resistance to eravacycline is estimated to be low as this is a new antibiotic with low resistance levels.

However, it is recognised that overall resistance not only has a direct impact on human and animal health, due to the failure in the treatment of infectious diseases, but also carries a heavy economic cost and leads to increasing healthcare costs, prolonged hospital stays, treatment failures and a significant number of deaths (European Commission 2017). In the EU it is estimated that 20,000 people die each year from an infection due to antibiotic-resistant bacteria and result in extra healthcare costs and productivity losses of at least €1.5 billion each year (ECDC & EMEA Joint Press Release 2009).

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table 18: SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age) Pseudomembranous colitis Emergence of resistance
Missing information	None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaire for permanent teeth discolouration:

Tooth discolouration follow-up form

A tooth discolouration follow-up form will be used to seek further details of any initial ADR reports of tooth discolouration (Annex 4). Information sought will include:

- whether exposure occurred during the 2nd or 3rd trimester of pregnancy, during maternal lactation or through exposure to the child
- whether there was exposure to any other tetracyclines
- details of any other adverse effects in the mouth

In the event that a case of delay in bone ossification processes is reported, the MAH commits to attempting to obtain detailed further information on the specific case.

Other forms of routine pharmacovigilance activities for pseudomembranous colitis:

Further characterisation of important risks in Phase 3 study in patients with cUTI (Study TP-434-021)

The important potential risk pseudomembranous colitis was quantified in a Phase 3 study as an adverse event of special interest (AESI). Study TP-434-021 is a Phase 3, randomised, double-blind, double-dummy, multicentre, prospective study assessing the efficacy and safety of i.v. eravacycline compared with ertapenem in complicated urinary tract infections. There were no reported events of pseudomembranous colitis in the TP-434-021 study. As the study was not initiated to specifically quantify the safety concern the study was not considered an additional pharmacovigilance activity.

III.2 Additional pharmacovigilance activities

Post-authorisation safety study (PASS) summary

Study short name and title:

Surveillance of the activity of Eravacycline against bacteria collected from USA, European and Asia-pacific hospitals from 2018 to 2022

Study NC-IHMA-2018-01

Rationale and study objectives:

Antimicrobial resistance is recognised as a global public health concern that requires surveillance for resistance patterns to various antimicrobials.

The 5-year study is evaluating antimicrobial resistance to eravacycline in Europe, USA and Asia/Pacific regions annually.

The objective of the study is the characterisation of the *in vitro* activity of eravacycline against a collection of currently circulating bacteria using minimum inhibitory concentration (MIC) determination according to the Clinical & Laboratory Standards Institute (CLSI) methodology.

Study design:

The study is designed to consecutively collect isolates predominantly from patients with intra-abdominal infections (IAI) or hospital-acquired pneumonia (HAP) from a total of 70-80 hospitals in Europe (40% of total), USA (40% of total) and Asia/Pacific (20% of total). If required target numbers cannot be reached, isolated from urinary tract infections (UTI) will be included.

All isolates will be collected each year from 2018 to 2022 (5 years in total) and will be from the IHMA repository.

Individual bacterial species are restricted to a maximum of 500 isolates per species. All isolates are tested using frozen 96-well MIC panels (broth microdilution in line with CLSI methodology) prepared at IHMA. The following organisms are included in the study:

- Enterobacteriaceae
- *Acinetobacter baumannii*
- *Stenotrophomonas maltophilia*
- *Haemophilus influenzae*
- *Staphylococcus spp.*
- *Enterococcus spp.*
- *Streptococcus spp.*

The antimicrobial agents and ranges for the indicated bacterial species are listed in the protocol (Annex 3). Quality control strains will be included in each test batch as recommended by CLSI.

Isolates will be collected between January and December of each year of testing. Susceptibility testing will be completed by the end of June of the following year. The final report will be issued in October of that year.

Data presented in the annual interim reports will include a line listing of MIC data, MIC_{50}, MIC_{90}, MIC minimum, MIC maximum and MIC range for each antimicrobial agent, MIC distributions (tabular and histograms) and QC results.

Study population:

Isolates predominantly from patients with IAI or HAP from 70-80 hospitals in Europe, USA and Asia/Pacific are included in the study. Isolates from patients with UTI will be included if the required target numbers cannot be reached. The target species and number of isolates (n=7,500 per annum) are summarised in Appendix A of the protocol (Annex 3).

Milestones:

Annual interim reports are provided in December every year for 5 years starting in December 2019. The fifth interim report (study completion) is to be submitted with the final report**.

III.3 Summary Table of additional Pharmacovigilance activities

Table 19: Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
Surveillance of the activity of Eravacycline against bacteria collected from USA, European and Asia-pacific hospitals from 2018 to 2022 Study NC-IHMA-2018-01 Ongoing	To evaluate the emergence of resistance of pathogens to eravacycline in hospitals in Europe, USA and Asia/Pacific regions	Emergence of resistance	Annual interim reports	Annual reports are provided in December every year for 5 years 1st Interim Report: Dec 2020 2nd Interim Report: Dec 2021 3rd Interim Report: Dec 2021* 4th Interim Report: Dec 2022 5th Interim Report: Dec 2023 (study completion)**
			Final report	Feb 2024**

* Two reports were submitted in 2021 (for data collected in 2018 and 2020). The 4th interim report presented data collected in 2021.
** Both reports to be submitted in Q2 2026.

Part IV: Plans for post-authorisation efficacy studies

No planned or ongoing post-authorisation efficacy studies are imposed for eravacycline.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 20: Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)	Routine risk communication: • Information in section 4.1 of the SmPC on the indication for use in adolescents from the age of 12 years weighing at least 50 kg and in adults. • Guidance in section 4.2 of the SmPC that the safety and efficacy of eravacycline have not been established in children less than 12 years of age or adolescents with body weight below 50 kg.. • Information in section 5.3 of the SmPC on the non-clinical findings. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Guidance in section 4.2 of the SmPC that Xerava should not be used in children aged under 8 years because of teeth discolouration. • Warning in section 4.4 of the SmPC that Xerava should not be used during tooth development (during the 2nd and 3rd trimester of pregnancy, and in children under 8 years of age) as it may cause permanent discolouration of the teeth (yellow-grey-brown). • Warning in section 4.6 of the SmPC that Xerava should not be used during pregnancy unless the clinical condition of the woman requires treatment as permanent dental defects and a delay in ossification processes may occur in the foetus with maternal exposure during the 2nd or 3rd trimester of pregnancy. • Warning in section 4.6 of the SmPC that long term use of other tetracyclines is not recommended because of the risk of dental discolouration and delay in ossification processes of the breast-fed infant and that the decision to breast-feed should take into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. • Information in section 1 of the PL on what Xerava is used for in adolescents from the age of 12 years weighing at least 50 kg and in adults. • Guidance in section 2 of the PL that Xerava must not be used in children below the age of 8 years because it can cause permanent effects on their teeth such as discolouration.

Safety concern	Routine risk minimisation activities
	• Guidance in section 2 of the PL for a patient to seek advice from their doctor before receiving Xerava if she is pregnant, thinks she may be pregnant or is planning to have a baby as eravacycline is not recommended for use during pregnancy as it can permanently stain the unborn child's teeth and delay the natural formation of the bones of the unborn child. • Guidance in section 2 of the PL for the patient to seek advice from their doctor before breast-feeding as it is not known if Xerava passes into breast milk but long-term use of other similar antibiotic medicines can stain the child's teeth permanently. Other routine risk minimisation measures beyond the Product Information: • Legal status (prescription only medicine)
Pseudomembranous colitis	Routine risk communication: • Listed as a class adverse reaction of antibiotics in section 4.8 of the SmPC. • Diarrhoea is listed as a side effect in section 4 of the PL. Routine risk minimisation activities recommending specific clinical measures to address the risk: • Warning in section 4.4 of the SmPC that antibiotic-associated colitis and pseudomembranous colitis have been reported with nearly all antibiotics and may be life-threatening. This diagnosis should be considered in patients with diarrhoea during or following eravacycline treatment with guidance to discontinue eravacycline and to use appropriate treatment. • Guidance in section 2 of the PL that patients should speak to their doctor or nurse if they are suffering from diarrhoea before taking Xerava and to tell their doctor straight away if they develop diarrhoea during or after treatment. Patients are advised not to take any medicine to treat diarrhoea without consulting their doctor first. Other routine risk minimisation measures beyond the Product Information: • Legal status (prescription only medicine)

Safety concern	Routine risk minimisation activities
Emergence of resistance	Routine risk communication: • Guidance in section 5.1 of the SmPC on the mechanism of resistance. Routine risk minimisation activities recommending specific clinical measures to address the risk: • None Other routine risk minimisation measures beyond the Product Information: • Legal status (prescription only medicine)

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Table 21: Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)	Routine risk minimisation measures: *SmPC section 4.1 where the indication for use in adolescents from the age of 12 years weighing at least 50 kg and in adults is presented* *SmPC section 4.2 where advice is given on use in children less than 12 years of age or adolescents with body weight below 50 kg SmPC section 4.2 where advice is given not to use in children under 8 years because of teeth discolouration* *SmPC section 4.4 where the risk of permanent teeth discolouration during the 2nd and 3rd trimester of pregnancy and in children under 8 years is highlighted* *SmPC section 4.6 where advice is given on risks associated with use during pregnancy and considerations for use* *SmPC section 4.6 where advice is given on risks associated with use during breast-feeding and considerations for use* *SmPC section 5.3 where information on non-clinical findings are provided* *PL section 1 where information is given on what Xerava is used for adolescents from the age of 12 years weighing at least 50 kg and in adults* *PL section 2 where advice is given on use in children and the permanent effects on teeth caused by tetracycline class antibiotics* *PL section 2 where advice is given on risks associated with use during pregnancy including permanent*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Tooth discolouration follow-up form* Additional pharmacovigilance activities: *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	staining of teeth and a delay in natural bone formation *PL section 2 where advice is given on risks associated with use during breast-feeding including permanent staining of teeth* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	
Pseudomembranous colitis	Routine risk minimisation measures: *SmPC section 4.4 where advice is given on the recommended action in case of pseudomembranous colitis* *Listed as a class adverse reaction of antibiotics in SmPC section 4.8* *PL section 2 where advice is given on the recommended action if symptoms occur* *Diarrhoea is listed as a side effect in PL section 4* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *Quantification in Phase 3 cUTI Study TP-434-021* Additional pharmacovigilance activities: *None*
Emergence of resistance	Routine risk minimisation measures: *SmPC section 5.1 where guidance is provided on the mechanism of resistance* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: *None* Additional pharmacovigilance activities: *Surveillance of the activity of Eravacycline against bacteria collected from USA, European and Asia-pacific hospitals from 2018 to 2022* *Study NC-IHMA-2018-01*

Part VI: Summary of the risk management plan

Summary of risk management plan for Xerava (eravacycline)

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

Xerava's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Xerava should be used.

This summary of the RMP for Xerava should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xerava's RMP.

I. The medicine and what it is used for

Xerava is authorised in adolescents from the age of 12 years weighing at least 50 kg, and in adults, for the treatment of complicated intra-abdominal infections (cIAI) (see SmPC for the full indication). It contains eravacycline as the active substance and it is given intravenously (through a drip into a vein).

Further information about the evaluation of Xerava's benefits can be found in Xerava's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/xerava

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Xerava, together with measures to minimise such risks and the proposed studies for learning more about Xerava's risks, 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 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 Xerava is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Xerava 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 proof of a link with the use of Xerava. 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);

List of important risks and missing information	
Important identified risks	None
Important potential risks	Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age) Pseudomembranous colitis Emergence of resistance
Missing information	None

II.B Summary of important risks

Important potential risk: Permanent teeth discolouration and a delay in ossification processes (foetal exposure in pregnancy during the 2nd and 3rd trimester, exposure to the breast-fed infant, and exposure in children under 8 years of age)	
Evidence for linking the risk to the medicine	Permanent teeth discolouration and a delay in ossification processes may occur in the foetus, breast-fed infant and child following maternal eravacycline treatment during the 2nd or 3rd trimester of pregnancy, through exposure to eravacycline through breast milk and in children under the age of 8 years, the time when the teeth and the bones are developing. These effects have not been observed with eravacycline in clinical studies but are known to occur with other tetracycline antibiotics through published studies in the medical literature[1, 2, 3], and therefore are expected to occur with eravacycline. Animal studies have shown that eravacycline can cross the placenta similarly to other tetracycline antibiotics, can cause a delay in ossification in the offspring of exposed animals and that eravacycline is excreted in breast milk.

Risk factors and risk groups	Infants whose mothers were taking eravacycline during the 2nd or 3rd trimester of pregnancy or who breast-feed from mothers taking eravacycline are at risk of permanent teeth discolouration and a delay in ossification processes. Children under the age of 8 years who take eravacycline are also at increased risk of these permanent effects.
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1 where the indication for use in adolescents from the age of 12 years weighing at least 50 kg and in adults is presented* *SmPC section 4.2 where advice is given on use in children below 12 years of age or adolescents with body weight below 50 kg* *SmPC section 4.2 where advice is given not to use in children under 8 years because of teeth discolouration* *SmPC section 4.4 where the risk of permanent teeth discolouration during the 2nd and 3rd trimester of pregnancy and in children under 8 years is highlighted* *SmPC section 4.6 where advice is given on risks associated with use during pregnancy and considerations for use* *SmPC section 4.6 where advice is given on risks associated with use during breast-feeding and considerations for use* *SmPC section 5.3 where information on non-clinical findings are provided* *PL section 1 where information is given on what Xerava is used for in adolescents from the age of 12 years weighing at least 50 kg and in adults* *PL section 2 where advice is given on use in children and the permanent effects on teeth caused by tetracycline class antibiotics* *PL section 2 where advice is given on risks associated with use during pregnancy including permanent staining of teeth and a delay in natural bone formation* *PL section 2 where advice is given on risks associated with use during breast-feeding including permanent staining of teeth* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Important potential risk: Pseudomembranous colitis	
Evidence for linking the risk to the medicine	Pseudomembranous colitis (*Clostridioides difficile*-associated diarrhoea) was not observed in patients treated with eravacycline in the clinical studies. However pseudomembranous colitis has been reported with nearly all antibacterial agents including the tetracyclines[4] and therefore is expected to occur in a small number of patients treated with eravacycline in clinical practice.
Risk factors and risk groups	Risk factors for pseudomembranous colitis include taking antibiotics, hospitalisation or residing in a nursing home, increasing age (especially over 65 years), a weakened immune system, a colon disease, such as inflammatory bowel disease or colorectal cancer, undergoing intestinal surgery and receiving chemotherapy treatment for cancer[5].
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4 where advice is given on the recommended action in case of pseudomembranous colitis* *Listed as a class adverse reaction of antibiotics in SmPC section 4.8* *PL section 2 where advice is given on the recommended action if symptoms occur* *Diarrhoea is listed as a side effect in PL section 4* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*

Important potential risk: Emergence of resistance	
Evidence for linking the risk to the medicine	Antimicrobial resistance is one of the most serious global public health threats in this century[6]. The appropriate use of antibiotics is essential for reducing and preventing antimicrobial resistance. As a novel, synthetic, broad-spectrum fluorocycline antibiotic, eravacycline is not expected to carry the same resistance as other widely used antibiotics, but as this may change, resistance levels need to be monitored through surveillance for resistance patterns.
Risk factors and risk groups	Antimicrobial resistance occurs naturally over time, usually through genetic changes but the misuse and overuse of antimicrobials in both humans and animals accelerates this process[7]. Poor infection control, inadequate sanitary conditions and inappropriate food-handling can encourage the spread of antimicrobial resistance[7]. Factors that may affect the development of antimicrobial resistance include dose, duration of treatment and class of antibiotic, disease transmission and exposure rates, host susceptibility (e.g., vaccination status), and transmissibility of the pathogen[8].

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 5.1 where guidance is provided on the mechanism of resistance* *Legal status (prescription only medicine)* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Surveillance of the activity of Eravacycline against bacteria collected from USA, European and Asia-pacific hospitals from 2018 to 2022* *Study NC-IHMA-2018-01:* See section II.C of this summary for an overview of the post-authorisation development plan.

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 Xerava.

II.C.2 Other studies in post-authorisation development plan

Surveillance of the activity of Eravacycline against bacteria collected from USA, European and Asia-pacific hospitals from 2018 to 2022

Study NC-IHMA-2018-01

Purpose of the study: Antimicrobial resistance is recognised as a global public health concern that requires surveillance for resistance patterns to various antimicrobials.

The 5-year study is evaluating antimicrobial resistance to eravacycline in Europe, USA and Asia/Pacific regions annually.

The objective of the study is the characterisation of the *in vitro* activity of eravacycline against a collection of currently circulating bacteria using minimum inhibitory concentration (MIC) determination according to the Clinical & Laboratory Standards Institute (CLSI) methodology.

References for the Summary of the risk management plan

[1]Watts A, Addy M. Tooth discolouration and staining: a review of the literature. Br Dent J. 2001 Mar 24;190(6):309-16.

[2]Cheng W, Yue Y, Fan W, et al. Effects of tetracyclines on bones: an ambiguous question needs to be clarified. Pharmazie. 2012 May;67(5):457-9.

[3]Conchie JM, Munroe JD, Anderson DO. The incidence of staining of permanent teeth by the tetracyclines. Can Med Assoc J. 1970 Aug 15;103(4):351-6.

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[7]World Health Organization (WHO). Antimicrobial resistance. Fact sheet September 2016.

[8]Friedman CR, Whitney CG. It's time for a change in practice: reducing antibiotic use can alter antibiotic resistance. J Infect Dis. 2008 Apr 15;197(8):1082-3.

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

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1. ADMINISTRATIVE DETAILS

Report Reference Number:

2. CHILD DETAILS

Patient initials:		
Age: years months	**Gender:** Male ☐ Female ☐	**Date of Birth**: (DD MMMYYYY)

3. EXPOSURE TO ERAVACYCLINE®

When was the child exposed to Eravacycline®:	☐ Via the mother (during pregnancy) When did the mother receive Eravacycline® (tick all that apply): ☐ *During the first trimester of pregnancy* Dose …… ☐*During the second trimester of pregnancy* Dose …… ☐ *During the third trimester of pregnancy* Dose …… Did the mother receive any other tetracycline antibiotic during pregnancy: ☐ *No* ☐ *Yes* *Please specify which tetracycline antibiotic:* ☐ *During the first trimester of pregnancy* Dose …… ☐*During the second trimester of pregnancy* Dose …… ☐ *During the third trimester of pregnancy* Dose …… ☐ Via the mother (via breastfeeding) Did the mother receive any other tetracycline during breastfeeding: ☐ *No* ☐ *Yes* *Please specify which tetracycline antibiotic:*

☐ As a patient themselves

How many times has the child received Eravacycline®:

☐ *Once*

Start date (DDMMMYYYY)	Stop date (DDMMMYYYY)	Dose

☐ *More than once*

Exposure # 1

Start date (DDMMMYYYY)	Stop date (DDMMMYYYY)	Dose

Exposure # 2

Start date (DDMMMYYYY)	Stop date (DDMMMYYYY)	Dose

4. HAS THE CHILD SUFFERED FROM DENTAL ISSUES

Tooth decay	☐		Early tooth loss	☐	Loose teeth ☐
Dry mouth	☐		Sensitive teeth	☐	Gum disease ☐
Other	☐	Please specify:			

5. HAS THE CHILD RECEIVED ANY OTHER MEDICATIONS SINCE BIRTH

None	☐		Other tetracycline antibiotic	☐	Corticosteroids ☐
Other tetracyclines	☐		Non-steroidal anti-inflammatories	☐	Antihistamine ☐

6. COMMENTS

Please provide a summary of the tooth discolouration, including location and number of affected teeth and provide photos of affected teeth if possible. Please state whether a Dentist has provided any comment/diagnosis on the tooth discolouration.

7. REPORTER DETAILS

Name:	Address:
Signature: Date:	Physician/Nurse ☐ Relative ☐ Dentist ☐ Pharmacist ☐ Other ☐ Please specify:

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Not applicable.