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 for the treatment of complicated intra-abdominal infections (cIAI) in adults (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 adult patients is presented *SmPC section 4.2 where advice is given on use in children and adolescents* *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 adult patients* *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.

[4]Treloar AJ, Hamlyn AN. Drug points: Pseudomembranous colitis and tetracycline. Br Med J (Clin Res Ed). 1987 Oct 17;295(6604):1001.

[5]Mayo Clinic. Pseudomembranous colitis. Symptoms and causes, Risk factors, Complications. 1998-2017 Mayo Foundation for Medical Education and Research (MFMER).

[6]Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. Pathog Glob Health. 2015;109(7):309-18.

[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.