ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xerava 50 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg eravacycline.

After reconstitution, each mL contains 10 mg eravacycline.
After further dilution, 1 mL contains 0.3 mg eravacycline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

Pale yellow to dark yellow cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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) (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

Posology

The recommended dose regimen is 1 mg/kg eravacycline every 12 hours for 4 to 14 days.

Strong CYP3A4 inducers
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 (see sections 4.4 and 4.5).

Elderly (≥ 65 years old)
No dose adjustment is required in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis. Eravacycline may be administered without regard to the timing of haemodialysis (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see sections 4.4, 4.5 and 5.2).

Paediatric population

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. Currently available data are described in section 4.8 but

no recommendation on a posology can be made. Xerava should not be used in children aged under 8 years because of the risk of tooth discolouration (see sections 4.4 and 4.6).

Method of administration

Intravenous use.

Xerava is administered only by intravenous infusion over approximately 1 hour (see section 4.4).

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

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
Hypersensitivity to tetracycline class antibiotics.

4.4 Special warnings and precautions for use

Anaphylactic reactions

Serious and occasionally fatal hypersensitivity reactions are possible and have been reported with other tetracycline class antibiotics (see section 4.3). In case of hypersensitivity reactions, treatment with eravacycline must be discontinued immediately and appropriate emergency measures must be initiated.

Clostridioides difficile-associated diarrhoea

Antibiotic-associated colitis and pseudomembranous colitis have been reported with the use of nearly all antibiotics and may range in severity from mild to life-threatening. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to treatment with eravacycline (see section 4.8). In such circumstances, the discontinuation of eravacycline and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Infusion-site reactions

Eravacycline is administered via intravenous infusion, using an infusion time of approximately 1 hour to minimise the risk of infusion-site reactions. Infusion-site erythema, pain/tenderness, phlebitis and thrombophlebitis were observed with intravenous eravacycline in clinical trials (see section 4.8). 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.

Non-susceptible micro-organisms

Prolonged use may result in the overgrowth of non-susceptible micro-organisms, including fungi. If superinfection occurs during therapy, it may require interruption of treatment. Other appropriate measures should be taken and alternative antimicrobial treatment should be considered in accordance with existing therapeutic guidelines.

Pancreatitis

Pancreatitis has been reported with eravacycline and has been severe in some cases (see section 4.8). If pancreatitis is suspected, eravacycline should be discontinued.

Paediatric population

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) (see section 4.6).

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 (see sections 4.2 and 4.5).

Patients with severe 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 (see section 4.8), particularly if these patients are obese and/or are also being treated with strong CYP3A inhibitors where the exposure may be further increased (see sections 4.5 and 5.2). In these cases, no recommendation on a posology can be made.

Limitations of the clinical data

In clinical trials in cIAI, there were no immunocompromised patients, and the majority of patients (80%) had APACHE II scores <10 at baseline; 5.4% of the patients had concurrent bacteraemia at baseline; 34% of the patients had complicated appendicitis.

Coagulopathy
Eravacycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT). Additionally, hypofibrinogenaemia has been reported with the use of eravacycline. Therefore, blood coagulation parameters such as PT or other suitable anticoagulation test, including blood fibrinogen, should be monitored prior to treatment initiation with eravacycline and regularly while on treatment.

4.5 Interaction with other medicinal products and other forms of interaction

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 intravenous q12h) when co-administered with rifampicin or other strong CYP3A inducers such as phenobarbital, carbamazepine, phenytoin and St. John's Wort (see sections 4.2 and 4.4).

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 (see sections 4.4 and 4.8).

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 (see section 5.2). Interactions with medicinal products that are substrates for these enzymes or transporters are therefore unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of eravacycline in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

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, due to accumulation in tissues with a high calcium turnover and formation of calcium chelate complexes (see sections 4.4 and 5.3). Xerava should not be used during pregnancy unless the clinical condition of the woman requires treatment with eravacycline.

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant while receiving eravacycline.

Breast-feeding

It is unknown whether eravacycline and its metabolites are excreted in human breast milk. Animal studies have shown excretion of eravacycline and its metabolites in breast milk (see section 5.3).

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.

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.

Fertility

There are no human data on the effect of eravacycline on fertility. Eravacycline did affect mating and fertility in male rats at clinically relevant exposures (see section 5.3).

4.7 Effects on ability to drive and use machines

Eravacycline may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of eravacycline (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In clinical trials, the most common adverse reactions in patients with cIAI treated with eravacycline (n=576) were nausea (3.0%), vomiting, infusion site phlebitis (each 1.9%), phlebitis (1.4%), infusion site thrombosis (0.9%), diarrhoea (0.7%), vessel puncture site erythema (0.5%), hyperhidrosis,

thrombophlebitis, infusion site hypoaesthesia, and headache (each 0.3%), which were generally mild or moderate in severity.

Tabulated list of adverse reactions

The adverse reactions identified with eravacycline are presented in Table 1. Adverse reactions are classified according to MedDRA system organ classification and frequency. Frequency categories are derived according to the following conventions: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Tabulated list of adverse reactions to eravacycline in clinical trials

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders	Hypofibrinogenaemia Increased international normalised ratio (INR) Prolonged activated partial thromboplastin time (aPTT) Prolonged prothrombin time (PT)	
Immune system disorders		Hypersensitivity
Nervous system disorders		Dizziness Headache
Vascular disorders	Thrombophlebitis[a] Phlebitis[b]	
Gastrointestinal disorders	Nausea Vomiting	Pancreatitis Diarrhoea
Hepatobiliary disorders		Aspartate aminotransferase (AST) increased Alanine aminotransferase (ALT) increased Hyperbilirubinaemia
Skin and subcutaneous tissue disorders		Rash Hyperhidrosis
General disorders and administration site conditions	Infusion site reaction[c]	

a. Thrombophlebitis includes the preferred terms thrombophlebitis and infusion site thrombosis
b. Phlebitis includes the preferred terms phlebitis, infusion site phlebitis, superficial phlebitis and injection site phlebitis
c. Infusion site reaction includes the preferred terms injection site erythema, infusion site hypoaesthesia, vessel puncture site erythema and vessel puncture site pain

Description of selected adverse reactions

Infusion site reactions
Mild to moderate infusion site reactions, including pain or discomfort, erythema and swelling or inflammation at the injection site as well as superficial thrombophlebitis and/or phlebitis have been reported in patients treated with eravacycline. Infusion site reactions can be mitigated by reducing the eravacycline infusion concentration or the infusion rate.

Tetracycline class effects
Tetracycline class adverse reactions include photosensitivity, *pseudotumor cerebri*, and anti-anabolic action which have led to increased blood urea nitrogen , azotaemia, acidosis, and hyperphosphataemia.

Diarrhoea
Antibiotic class adverse reactions include pseudomembranous colitis, and overgrowth of non-susceptible organisms, including fungi (see section 4.4). In clinical trials, treatment-related diarrhoea occurred in 0.7% of patients; all cases were mild in severity.

Paediatric Population

In a phase I study to determine the pharmacokinetics and the safety of a single dose of intravenous eravacycline in children aged 8 to less than 18 years (n= 19, with 10 less than 12 years old) the most frequently reported adverse reactions were nausea (26.3%), vomiting (15.8%), headache (15.8%), and hyperhidrosis (10.5%). In general, adverse reactions were mild or moderate in severity and similar to the adverse reactions observed in adults. Two events were assessed as severe including one event of anaphylactic reaction and one event of pleural effusion, which was also assessed as serious.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In trials administering up to 3 mg/kg eravacycline to healthy volunteers it has been observed that doses higher than the recommended dose lead to a higher rate of nausea and vomiting.

In the case of suspected overdose Xerava should be discontinued and the patient monitored for adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, tetracyclines, ATC code: J01AA13.

Mechanism 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.

Mechanism of resistance

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.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for eravacycline and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Pharmacokinetic/pharmacodynamic relationship

The area under the plasma concentration-time curve (AUC) divided by the minimum inhibitory concentration (MIC) of eravacycline has been shown to be the best predictor of efficacy *in vitro*, utilising human steady state exposures in a chemostat and confirmed *in vivo* in animal models of infection.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical trials against the pathogens listed for cIAI that were susceptible to eravacycline *in vitro*:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- Viridans *Streptococcus spp.*

Antibacterial activity against other relevant pathogens

In vitro data indicate that the following pathogen is not susceptible to eravacycline:

- *Pseudomonas aeruginosa*

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of trials with Xerava in one or more subsets of the paediatric population in cIAI (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Eravacycline is administered intravenously and therefore has 100% bioavailability.

The mean pharmacokinetic parameters of eravacycline after single and multiple intravenous infusions (60 minutes) of 1 mg/ kg administered to healthy adults every 12 hours are presented in Table 2.

Table 2 Mean (%CV) plasma pharmacokinetic parameters of eravacycline after single and multiple intravenous infusions to healthy adults

Eravacycline dosing		PK parameters arithmetic mean (%CV)			
		C_{max} (ng/mL)	t_{max}[a] (h)	AUC_{0-12}[b] (ng*h/mL)	$t_{1/2}$ (h)
1.0 mg/kg intravenous every 12 hours (n=6)	Day 1	2125 (15)	1.0 (1.0-1.0)	4305 (14)	9 (21)
	Day 10	1825 (16)	1.0 (1.0-1.0)	6309 (15)	39 (32)

[a] Mean (range) represented

[b] AUC of Day 1 = AUC_{0-12} after the first dose and AUC for Day 10 = steady state AUC_{0-12}

Distribution

The *in vitro* binding of eravacycline to human plasma proteins increases with increasing concentrations, with 79%, 86% and 90% (bound) at 0.1, 1 and10 μg/mL, respectively. The mean (%CV) volume of distribution at steady-state in healthy normal volunteers following 1 mg/kg every 12h is approximately 321 L (6.35), which is greater than total body water.

Biotransformation

Unchanged eravacycline is the major medicinal product-related component in human plasma and human urine. Eravacycline is metabolised primarily by CYP3A4- and FMO-mediated oxidation of the pyrrolidine ring to TP-6208, and by chemical epimerisation at C-4 to TP-498. Additional minor metabolites are formed by glucuronidation, oxidation and hydrolysis. TP-6208 and TP-498 are not considered to be pharmacologically active.

Eravacycline is a substrate for the transporters P-gp, OATP1B1 and OATP1B3 but not for BCRP.

Elimination

Eravacycline is excreted in both urine and faeces. Renal clearance and biliary and direct intestinal excretion account for approximately 35% and 48% of total body clearance after administration of a single intravenous dose of 60 mg ^{14}C-eravacycline, respectively.

Linearity/non-linearity

The C_{max} and AUC of eravacycline in healthy adults increase approximately in proportion to an increase in dose. There is approximately a 45% accumulation following intravenous dosing of 1 mg/kg every 12 hours.

Within the range of eravacycline multiple intravenous doses studied clinically, the pharmacokinetic parameters AUC and C_{max} demonstrate linearity, but with increasing doses the increase in both AUC and C_{max} are slightly less than dose-proportional.

Potential for drug-drug interactions

Eravacycline and its metabolites are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 *in vitro*. Eravacycline, TP-498 and TP-6208 are not inducers of CYP1A2, CYP2B6 or CYP3A4.

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*.

Special populations

Renal impairment
The geometric least square mean C_{max} for eravacycline was increased by 8.8% for subjects with end stage renal disease (ESRD) versus healthy subjects with 90% CI -19.4, 45.2. The geometric least square mean $AUC_{0\text{-}inf}$ for eravacycline was decreased by 4.0% for subjects with ESRD versus healthy subjects with 90% CI -14.0, 12.3.

Hepatic impairment
The geometric mean C_{max} for eravacycline was increased by 13.9%, 16.3%, and 19.7% for subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment versus healthy subjects, respectively. The geometric mean $AUC_{0\text{-}inf}$ for eravacycline was increased by 22.9%, 37.9%, and 110.3% for subjects with mild, moderate, and severe hepatic impairment versus healthy subjects, respectively.

Gender
In a population pharmacokinetic analysis of eravacycline, no clinically relevant differences in AUC by gender were observed for eravacycline.

Elderly (≥ 65 years)
In a population pharmacokinetic analysis of eravacycline, no clinically relevant differences in the pharmacokinetics of eravacycline were observed with respect to age.

Paediatric population
A popPK study was conducted. This was inconclusive and consequently the dose in children below 12 years / 50 kg could not be determined. Adolescents (12-17 years) weighing at least 50 kg are expected to have comparable exposure to adults when treated with 1 mg/kg every 12 hours.

Body weight
In a population pharmacokinetic analysis it was shown that eravacycline disposition (clearance and volume) was dependent on body weight. However, the resulting difference in exposure to eravacycline in terms of AUC does not warrant dose adjustments in the weight range studied. No data are available for patients weighing more than 137 kg. The potential influence of severe obesity on eravacycline exposure has not been studied.

5.3 Preclinical safety data

In repeated dose toxicity studies in rats, dogs and monkeys, lymphoid depletion/atrophy of lymph nodes, spleen and thymus, decreased erythrocytes, reticulocytes, leukocytes, and platelets (dog and monkey), in association with bone marrow hypocellularity, and adverse gastrointestinal effects (dog and monkey) were observed with eravacycline. These findings were reversible or partially reversible during recovery periods of 3- to 7-weeks.

Bone discolouration (in the absence of histological findings), which was not fully reversible over recovery periods of up to 7-weeks, was observed in rats and monkeys after 13 weeks of dosing.

Intravenous administration of high doses of eravacycline has been associated with cutaneous responses (including hives, scratching, swelling, and/or skin erythema) in rat and dog studies.

In fertility studies in male rats, eravacycline administered at about 5 times the clinical exposure (based on AUC), gave rise to a significantly reduced number of pregnancies. These findings were reversible following a 70-day (10-week) recovery period, equivalent to a spermatogenic cycle in the rat. Findings on the male reproductive organs were also observed in rats in the repeated dose toxicity studies for 14 days or 13 weeks at exposures more than 10- or 5-fold the clinical exposure based on AUC. The observations included degeneration of the seminiferous tubules, oligospermia, and cellular debris in the epididymides, spermatid retention in the seminiferous tubules, increase of spermatid head retention

in Sertoli cells, and vacuolation of Sertoli cells and decreased sperm counts. No adverse effects on mating or fertility were observed in female rats.

In embryo-foetal studies, no adverse effects were observed in rats at exposures comparable to clinical exposure or in rabbits at exposures 1.9-fold higher than the clinical exposure (based on AUC) in rats and rabbits respectively. Doses more than 2- or 4-fold higher than the clinical exposure (based on AUC) were associated with maternal toxicity (clinical observations and reduced body weight gain and food consumption), and reduced foetal body weights and delays in skeletal ossification in both species and abortion in the rabbit.

Animal studies indicate that eravacycline crosses the placenta and is found in foetal plasma. Eravacycline (and metabolites) is excreted in the milk of lactating rats.

Eravacycline is not genotoxic. Carcinogenicity studies with eravacycline have not been conducted.

Xerava may have the potential to be very persistent in freshwater sediment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Chemical and physical in-use stability after reconstitution in the vial has been demonstrated for 1 hour at 25 °C.

Chemical and physical in-use stability after dilution has been demonstrated for 72 hours at 2 °C – 8 °C and 12 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 72 hours at 2 °C – 8 °C, unless the method of reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Keep the vial in the carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL Type I glass vial with chlorobutyl rubber stopper and aluminium cap.

Pack sizes: 1 vial and multipacks containing 12 (12 packs of 1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General precautions

Each vial is for single use only.

Aseptic technique must be followed when preparing the infusion solution.

Instructions for reconstitution
The contents of the required number of vials should each be reconstituted with 5 mL water for injections, and swirled gently until the powder has dissolved entirely. Shaking or rapid movement should be avoided as it may cause foaming.

Reconstituted Xerava should be a clear, pale yellow to orange solution. The solution should not be used if any particles are noticed or the solution is cloudy.

Preparation of the infusion 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. See example calculations in Table 3 (adults) and Table 4 (adolescents 12 - 17 years).

Gently invert the bag to mix the solution.

Table 3 Example calculations for adult patients weighing 40 kg to 200 kg[1]

Patient weight (kg)	Total dose (mg)	Number of vials to needed to reconstitute	Total volume to be diluted (mL)	Recommended infusion bag size (mL)
40	40	1	4	100
60	60	2	6	250
80	80	2	8	250
100	100	2	10	250
150	150	3	15	500
200	200	4	20	500

[1] The exact dose needs to be calculated based on the specific patient weight.

For adult patients weighing **≥ 40 kg – < 50 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 100 mL infusion bag.

For adult patients weighing **50 kg – 100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

For adult patients weighing >**100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 500 mL infusion bag.

Table 4 Example calculations for adolescent patients (12 - 17 years) weighing 50 kg to 90 kg[1]

Patient weight (kg)	Total dose (mg)	Number of vials to needed to reconstitute	Total volume to be diluted (mL)	Recommended infusion bag size (mL)
50	50	1	5	250
60	60	2	6	250
70	70	2	7	250
80	80	2	8	250
90	90	2	9	250

[1] The exact dose needs to be calculated based on the specific patient weight.

For adolescent patients weighing **50 kg – 90 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

Infusion
The ready to use solution should be inspected visually for particulate matter prior to administration. Reconstituted and diluted solutions containing visible particles or that are cloudy in appearance should be discarded.

Following dilution, Xerava is administered intravenously over approximately 1 hour.

The reconstituted and diluted solution must be administered as an intravenous infusion only. It must not be administered as an intravenous bolus.

If the same intravenous line is used for sequential infusion of several different medicinal products, the line should be flushed before and after infusion with sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/001
EU/1/18/1312/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018
Date of latest renewal: 12 April 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Xerava 100 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg eravacycline.

After reconstitution, each mL contains 20 mg eravacycline.
After further dilution, 1 mL contains 0.6 mg eravacycline.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

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

Pale yellow to dark yellow cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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) (see sections 4.4 and 5.1).

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

4.2 Posology and method of administration

Posology

The recommended dose regimen is 1 mg/kg eravacycline every 12 hours for 4 to 14 days.

Strong CYP3A4 inducers
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 (see sections 4.4 and 4.5).

Elderly (≥ 65 years old)
No dose adjustment is required in elderly patients (see section 5.2).

Renal impairment
No dose adjustment is necessary in patients with renal impairment or in patients undergoing haemodialysis. Eravacycline may be administered without regard to the timing of haemodialysis (see section 5.2).

Hepatic impairment
No dose adjustment is necessary in patients with hepatic impairment (see sections 4.4, 4.5 and 5.2).

Paediatric population

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. Currently available data are described in section 4.8 but

no recommendation on a posology can be made. Xerava should not be used in children aged under 8 years because of the risk of tooth discolouration (see sections 4.4 and 4.6).

Method of administration

Intravenous use.

Xerava is administered only by intravenous infusion over approximately 1 hour (see section 4.4).

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

4.3 Contraindications

Hypersensitivity to the active substance, or to any of the excipients listed in section 6.1.
Hypersensitivity to tetracycline class antibiotics.

4.4 Special warnings and precautions for use

Anaphylactic reactions

Serious and occasionally fatal hypersensitivity reactions are possible and have been reported with other tetracycline class antibiotics (see section 4.3). In case of hypersensitivity reactions, treatment with eravacycline must be discontinued immediately and appropriate emergency measures must be initiated.

Clostridioides difficile-associated diarrhoea

Antibiotic-associated colitis and pseudomembranous colitis have been reported with the use of nearly all antibiotics and may range in severity from mild to life-threatening. It is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to treatment with eravacycline (see section 4.8). In such circumstances, the discontinuation of eravacycline and the use of supportive measures together with the administration of specific treatment for *Clostridioides difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Infusion-site reactions

Eravacycline is administered via intravenous infusion, using an infusion time of approximately 1 hour to minimise the risk of infusion-site reactions. Infusion-site erythema, pain/tenderness, phlebitis and thrombophlebitis were observed with intravenous eravacycline in clinical trials (see section 4.8). 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.

Non-susceptible micro-organisms

Prolonged use may result in the overgrowth of non-susceptible micro-organisms, including fungi. If superinfection occurs during therapy, it may require interruption of treatment. Other appropriate measures should be taken and alternative antimicrobial treatment should be considered in accordance with existing therapeutic guidelines.

Pancreatitis

Pancreatitis has been reported with eravacycline and has been severe in some cases (see section 4.8). If pancreatitis is suspected, eravacycline should be discontinued.

Paediatric population

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) (see section 4.6).

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 (see sections 4.2 and 4.5).

Patients with severe 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 (see section 4.8), particularly if these patients are obese and/or are also being treated with strong CYP3A inhibitors where the exposure may be further increased (see sections 4.5 and 5.2). In these cases, no recommendation on a posology can be made.

Limitations of the clinical data

In clinical trials in cIAI, there were no immunocompromised patients, and the majority of patients (80%) had APACHE II scores <10 at baseline; 5.4% of the patients had concurrent bacteraemia at baseline; 34% of the patients had complicated appendicitis.

Coagulopathy
Eravacycline may prolong both prothrombin time (PT) and activated partial thromboplastin time (aPTT). Additionally, hypofibrinogenaemia has been reported with the use of eravacycline. Therefore, blood coagulation parameters such as PT or other suitable anticoagulation test, including blood fibrinogen, should be monitored prior to treatment initiation with eravacycline and regularly while on treatment.

4.5 Interaction with other medicinal products and other forms of interaction

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 intravenous q12h) when co-administered with rifampicin or other strong CYP3A inducers such as phenobarbital, carbamazepine, phenytoin and St. John's Wort (see sections 4.2 and 4.4).

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 (see sections 4.4 and 4.8).

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 (see section 5.2). Interactions with medicinal products that are substrates for these enzymes or transporters are therefore unlikely.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of eravacycline in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

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, due to accumulation in tissues with a high calcium turnover and formation of calcium chelate complexes (see sections 4.4 and 5.3). Xerava should not be used during pregnancy unless the clinical condition of the woman requires treatment with eravacycline.

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant while receiving eravacycline.

Breast-feeding

It is unknown whether eravacycline and its metabolites are excreted in human breast milk. Animal studies have shown excretion of eravacycline and its metabolites in breast milk (see section 5.3).

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.

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.

Fertility

There are no human data on the effect of eravacycline on fertility. Eravacycline did affect mating and fertility in male rats at clinically relevant exposures (see section 5.3).

4.7 Effects on ability to drive and use machines

Eravacycline may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of eravacycline (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

In clinical trials, the most common adverse reactions in patients with cIAI treated with eravacycline (n=576) were nausea (3.0%), vomiting, infusion site phlebitis (each 1.9%), phlebitis (1.4%), infusion site thrombosis (0.9%), diarrhoea (0.7%), vessel puncture site erythema (0.5%), hyperhidrosis,

thrombophlebitis, infusion site hypoaesthesia, and headache (each 0.3%), which were generally mild or moderate in severity.

Tabulated list of adverse reactions

The adverse reactions identified with eravacycline are presented in Table 1. Adverse reactions are classified according to MedDRA system organ classification and frequency. Frequency categories are derived according to the following conventions: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1 Tabulated list of adverse reactions to eravacycline in clinical trials

System Organ Class	Common	Uncommon
Blood and lymphatic system disorders	Hypofibrinogenaemia Increased international normalised ratio (INR) Prolonged activated partial thromboplastin time (aPTT) Prolonged prothrombin time (PT)	
Immune system disorders		Hypersensitivity
Nervous system disorders		Dizziness Headache
Vascular disorders	Thrombophlebitis[a] Phlebitis[b]	
Gastrointestinal disorders	Nausea Vomiting	Pancreatitis Diarrhoea
Hepatobiliary disorders		Aspartate aminotransferase (AST) increased Alanine aminotransferase (ALT) increased Hyperbilirubinaemia
Skin and subcutaneous tissue disorders		Rash Hyperhidrosis
General disorders and administration site conditions	Infusion site reaction[c]	

a. Thrombophlebitis includes the preferred terms thrombophlebitis and infusion site thrombosis
b. Phlebitis includes the preferred terms phlebitis, infusion site phlebitis, superficial phlebitis and injection site phlebitis
c. Infusion site reaction includes the preferred terms injection site erythema, infusion site hypoaesthesia, vessel puncture site erythema and vessel puncture site pain

Description of selected adverse reactions

Infusion site reactions
Mild to moderate infusion site reactions, including pain or discomfort, erythema and swelling or inflammation at the injection site as well as superficial thrombophlebitis and/or phlebitis have been reported in patients treated with eravacycline. Infusion site reactions can be mitigated by reducing the eravacycline infusion concentration or the infusion rate.

Tetracycline class effects
Tetracycline class adverse reactions include photosensitivity, *pseudotumor cerebri*, and anti-anabolic action which have led to increased blood urea nitrogen, azotaemia, acidosis, and hyperphosphataemia.

Diarrhoea
Antibiotic class adverse reactions include pseudomembranous colitis, and overgrowth of non-susceptible organisms, including fungi (see section 4.4). In clinical trials, treatment-related diarrhoea occurred in 0.7% of patients; all cases were mild in severity.

Paediatric Population

In a phase I study to determine the pharmacokinetics and the safety of a single dose of intravenous eravacycline in children aged 8 to less than 18 years (n= 19, with 10 less than 12 years old) the most frequently reported adverse reactions were nausea (26.3%), vomiting (15.8%), headache (15.8%), and hyperhidrosis (10.5%). In general, adverse reactions were mild or moderate in severity and similar to the adverse reactions observed in adults. Two events were assessed as severe including one event of anaphylactic reaction and one event of pleural effusion, which was also assessed as serious.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In trials administering up to 3 mg/kg eravacycline to healthy volunteers it has been observed that doses higher than the recommended dose lead to a higher rate of nausea and vomiting.

In the case of suspected overdose Xerava should be discontinued and the patient monitored for adverse reactions.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, tetracyclines, ATC code: J01AA13.

Mechanism 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.

Mechanism of resistance

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.

Susceptibility testing breakpoints

MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for eravacycline and are listed here:
https://www.ema.europa.eu/documents/other/minimum-inhibitory-concentration-mic-breakpoints_en.xlsx

Pharmacokinetic/pharmacodynamic relationship

The area under the plasma concentration-time curve (AUC) divided by the minimum inhibitory concentration (MIC) of eravacycline has been shown to be the best predictor of efficacy *in vitro*, utilising human steady state exposures in a chemostat and confirmed *in vivo* in animal models of infection.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical trials against the pathogens listed for cIAI that were susceptible to eravacycline *in vitro*:

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Staphylococcus aureus*
- *Enterococcus faecalis*
- *Enterococcus faecium*
- Viridans *Streptococcus spp.*

Antibacterial activity against other relevant pathogens

In vitro data indicate that the following pathogen is not susceptible to eravacycline:
- *Pseudomonas aeruginosa*

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of trials with Xerava in one or more subsets of the paediatric population in cIAI (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Eravacycline is administered intravenously and therefore has 100% bioavailability.

The mean pharmacokinetic parameters of eravacycline after single and multiple intravenous infusions (60 minutes) of 1 mg/ kg administered to healthy adults every 12 hours are presented in Table 2.

Table 2 Mean (%CV) plasma pharmacokinetic parameters of eravacycline after single and multiple intravenous infusions to healthy adults

Eravacycline dosing		**PK parameters arithmetic mean (%CV)**			
		C_{max} (ng/mL)	**t_{max}[a] (h)**	**AUC_{0-12}[b] (ng*h/mL)**	**$t_{1/2}$ (h)**
1.0 mg/kg intravenous every 12 hours (n=6)	Day 1	2125 (15)	1.0 (1.0-1.0)	4305 (14)	9 (21)
	Day 10	1825 (16)	1.0 (1.0-1.0)	6309 (15)	39 (32)

[a] Mean (range) represented
[b] AUC of Day 1 = AUC_{0-12} after the first dose and AUC for Day 10 = steady state AUC_{0-12}

Distribution

The *in vitro* binding of eravacycline to human plasma proteins increases with increasing concentrations, with 79%, 86% and 90% (bound) at 0.1, 1 and10 µg/mL, respectively. The mean (%CV) volume of distribution at steady-state in healthy normal volunteers following 1 mg/kg every 12h is approximately 321 L (6.35), which is greater than total body water.

Biotransformation

Unchanged eravacycline is the major medicinal product-related component in human plasma and human urine. Eravacycline is metabolised primarily by CYP3A4- and FMO-mediated oxidation of the pyrrolidine ring to TP-6208, and by chemical epimerisation at C-4 to TP-498. Additional minor metabolites are formed by glucuronidation, oxidation and hydrolysis. TP-6208 and TP-498 are not considered to be pharmacologically active.

Eravacycline is a substrate for the transporters P-gp, OATP1B1 and OATP1B3 but not for BCRP.

Elimination

Eravacycline is excreted in both urine and faeces. Renal clearance and biliary and direct intestinal excretion account for approximately 35% and 48% of total body clearance after administration of a single intravenous dose of 60 mg ^{14}C-eravacycline, respectively.

Linearity/non-linearity

The C_{max} and AUC of eravacycline in healthy adults increase approximately in proportion to an increase in dose. There is approximately a 45% accumulation following intravenous dosing of 1 mg/kg every 12 hours.

Within the range of eravacycline multiple intravenous doses studied clinically, the pharmacokinetic parameters AUC and C_{max} demonstrate linearity, but with increasing doses the increase in both AUC and C_{max} are slightly less than dose-proportional.

Potential for drug-drug interactions

Eravacycline and its metabolites are not inhibitors of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP3A4 *in vitro*. Eravacycline, TP-498 and TP-6208 are not inducers of CYP1A2, CYP2B6 or CYP3A4.

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*.

Special populations

Renal impairment
The geometric least square mean C_{max} for eravacycline was increased by 8.8% for subjects with end stage renal disease (ESRD) versus healthy subjects with 90% CI -19.4, 45.2. The geometric least square mean $AUC_{0\text{-}inf}$ for eravacycline was decreased by 4.0% for subjects with ESRD versus healthy subjects with 90% CI -14.0, 12.3.

Hepatic impairment
The geometric mean C_{max} for eravacycline was increased by 13.9%, 16.3%, and 19.7% for subjects with mild (Child-Pugh Class A), moderate (Child-Pugh Class B), and severe (Child-Pugh Class C) hepatic impairment versus healthy subjects, respectively. The geometric mean $AUC_{0\text{-}inf}$ for

eravacycline was increased by 22.9%, 37.9%, and 110.3% for subjects with mild, moderate, and severe hepatic impairment versus healthy subjects, respectively.

Gender
In a population pharmacokinetic analysis of eravacycline, no clinically relevant differences in AUC by gender were observed for eravacycline.

Elderly (≥ 65 years)
In a population pharmacokinetic analysis of eravacycline, no clinically relevant differences in the pharmacokinetics of eravacycline were observed with respect to age.

Paediatric population
A popPK study was conducted. This was inconclusive and consequently the dose in children below 12 years / 50 kg could not be determined. Adolescents (12-17 years) weighing at least 50 kg are expected to have comparable exposure to adults when treated with 1 mg/kg every 12 hours.

Body weight
In a population pharmacokinetic analysis it was shown that eravacycline disposition (clearance and volume) was dependent on body weight. However, the resulting difference in exposure to eravacycline in terms of AUC does not warrant dose adjustments in the weight range studied. No data are available for patients weighing more than 137 kg. The potential influence of severe obesity on eravacycline exposure has not been studied.

5.3 Preclinical safety data

In repeated dose toxicity studies in rats, dogs and monkeys, lymphoid depletion/atrophy of lymph nodes, spleen and thymus, decreased erythrocytes, reticulocytes, leukocytes, and platelets (dog and monkey), in association with bone marrow hypocellularity, and adverse gastrointestinal effects (dog and monkey) were observed with eravacycline. These findings were reversible or partially reversible during recovery periods of 3- to 7-weeks.

Bone discolouration (in the absence of histological findings), which was not fully reversible over recovery periods of up to 7-weeks, was observed in rats and monkeys after 13 weeks of dosing.

Intravenous administration of high doses of eravacycline has been associated with cutaneous responses (including hives, scratching, swelling, and/or skin erythema) in rat and dog studies.

In fertility studies in male rats, eravacycline administered at about 5 times the clinical exposure (based on AUC), gave rise to a significantly reduced number of pregnancies. These findings were reversible following a 70-day (10-week) recovery period, equivalent to a spermatogenic cycle in the rat. Findings on the male reproductive organs were also observed in rats in the repeated dose toxicity studies for 14 days or 13 weeks at exposures more than 10- or 5-fold the clinical exposure based on AUC. The observations included degeneration of the seminiferous tubules, oligospermia, and cellular debris in the epididymides, spermatid retention in the seminiferous tubules, increase of spermatid head retention in Sertoli cells, and vacuolation of Sertoli cells and decreased sperm counts. No adverse effects on mating or fertility were observed in female rats.

In embryo-foetal studies, no adverse effects were observed in rats at exposures comparable to clinical exposure or in rabbits at exposures 1.9-fold higher than the clinical exposure (based on AUC) in rats and rabbits respectively. Doses more than 2- or 4-fold higher than the clinical exposure (based on AUC) were associated with maternal toxicity (clinical observations and reduced body weight gain and food consumption), and reduced foetal body weights and delays in skeletal ossification in both species and abortion in the rabbit.

Animal studies indicate that eravacycline crosses the placenta and is found in foetal plasma. Eravacycline (and metabolites) is excreted in the milk of lactating rats.

Eravacycline is not genotoxic. Carcinogenicity studies with eravacycline have not been conducted.

Xerava may have the potential to be very persistent in freshwater sediment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years

Chemical and physical in-use stability after reconstitution in the vial has been demonstrated for 1 hour at 25 °C.
Chemical and physical in-use stability after dilution has been demonstrated for 72 hours at 2 °C - 8 °C and 12 hours at 25 °C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 72 hours at 2 °C – 8 °C, unless the method of reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C–8°C). Keep the vial in the carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 mL Type I glass vial with butyl rubber stopper and aluminium cap.

Pack sizes: 1 vial, 10 vials and multipacks containing 12 (12 packs of 1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

General precautions

Each vial is for single use only.

Aseptic technique must be followed when preparing the infusion solution.

Instructions for reconstitution
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, and swirled gently

until the powder has dissolved entirely. Shaking or rapid movement should be avoided as it may cause foaming.

Reconstituted Xerava should be a clear, pale yellow to orange solution. The solution should not be used if any particles are noticed or the solution is cloudy.

Preparation of the infusion 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. See example calculations in Table 3 (adults) and Table 4 (adolescents 12 - 17 years).

Gently invert the bag to mix the solution.

Table 3Example calculations for adult patients weighing 40 kg to 200 kg[1]

Patient weight (kg)	**Total dose (mg)**	**Number of vials to needed to reconstitute**	**Total volume to be diluted (mL)**	**Recommended infusion bag size (mL)**
40	40	1	2	100
60	60	1	3	250
80	80	1	4	250
100	100	1	5	250
150	150	2	7.5	500
200	200	2	10	500

[1] The exact dose needs to be calculated based on the specific patient weight.

For adult patients weighing **≥ 40 kg – < 50 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 100 mL infusion bag.

For adult patients weighing **50 kg – 100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

For adult patients weighing >**100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 500 mL infusion bag.

Table 4 Example calculations for adolescent patients (12-17 years) weighing 50 kg to 90 kg[1]

Patient weight (kg)	Total dose (mg)	Number of vials to needed to reconstitute	Total volume to be diluted (mL)	Recommended infusion bag size (mL)
50	50	1	2.5	250
60	60	1	3	250
70	70	1	3.5	250
80	80	1	4	250
90	90	1	4.5	250

[1] The exact dose needs to be calculated based on the specific patient weight.

For adolescent patients weighing **50 kg – 90 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

Infusion
The ready to use solution should be inspected visually for particulate matter prior to administration. Reconstituted and diluted solutions containing visible particles or that are cloudy in appearance should be discarded.

Following dilution, Xerava is administered intravenously over approximately 1 hour.

The reconstituted and diluted solution must be administered as an intravenous infusion only. It must not be administered as an intravenous bolus.

If the same intravenous line is used for sequential infusion of several different medicinal products, the line should be flushed before and after infusion with sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal

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

7. MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/003
EU/1/18/1312/004
EU/1/18/1312/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2018
Date of latest renewal: 12 April 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

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

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Xerava 100mg powder for concentrate for solution for infusion

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

PAION Deutschland GmbH
Heussstraße 25
52078 Aachen
Germany

Xerava 50mg powder for concentrate for solution for infusion

Patheon Italia S.p.A.
2° Trav. SX. Via Morolense, 5
03013 Ferentino (FR)
Italy

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON: 1 VIAL

1. NAME OF THE MEDICINAL PRODUCT

Xerava 50 mg powder for concentrate for solution for infusion
eravacycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg eravacycline,
After reconstitution, 1 mL contains 10 mg eravacycline.

3. LIST OF EXCIPIENTS

mannitol (E421), sodium hydroxide, hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
for intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON: MULTIPACK, CONTAINS BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Xerava 50 mg powder for concentrate for solution for infusion
eravacycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg eravacycline,
After reconstitution, 1 mL contains 10 mg eravacycline.

3. LIST OF EXCIPIENTS

mannitol (E421), sodium hydroxide, hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
Multipack: 12 (12x1) vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
for intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the inner carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

INNER CARTON: MULTIPACK, CONTAINS NO BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Xerava 50 mg powder for concentrate for solution for infusion
eravacycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg eravacycline,
After reconstitution, 1 mL contains 10 mg eravacycline.

3. LIST OF EXCIPIENTS

mannitol (E421), sodium hydroxide, hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
for intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Xerava 50 mg powder for concentrate
eravacycline
IV after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON: 1 VIAL, 10 VIALS

1. NAME OF THE MEDICINAL PRODUCT

Xerava 100 mg powder for concentrate for solution for infusion
eravacycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg eravacycline,
After reconstitution, 1 mL contains 20 mg eravacycline.

3. LIST OF EXCIPIENTS

mannitol (E421), sodium hydroxide, hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
for intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/003 1 vial
EU/1/18/1312/005 10 vials

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON: MULTIPACK, CONTAINS BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Xerava 100 mg powder for concentrate for solution for infusion
eravacycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg eravacycline,
After reconstitution, 1 mL contains 20 mg eravacycline.

3. LIST OF EXCIPIENTS

mannitol (E421), sodium hydroxide, hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
Multipack: 12 (12x1) vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
for intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the inner carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

INNER CARTON: MULTIPACK, CONTAINS NO BLUE BOX

1. NAME OF THE MEDICINAL PRODUCT

Xerava 100 mg powder for concentrate for solution for infusion
eravacycline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg eravacycline,
After reconstitution, 1 mL contains 20 mg eravacycline.

3. LIST OF EXCIPIENTS

mannitol (E421), sodium hydroxide, hydrochloric acid.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
for intravenous use after reconstitution and dilution

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Keep the vial in the carton in order to protect from light.

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1312/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Xerava 100 mg powder for concentrate
eravacycline
IV after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xerava 50 mg powder for concentrate for solution for infusion
eravacycline

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Xerava is and what it is used for

What Xerava is

Xerava is an antibiotic medicine that contains the active substance eravacycline. It belongs to a group of antibiotics called 'tetracyclines' which work by stopping the growth of certain infectious bacteria.

What Xerava is used for

Xerava is used to treat adolescents from the age of 12 years weighing at least 50 kg, and adults, with a complicated infection in the abdomen.

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

You must not receive Xerava

- if you are allergic to eravacycline or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to any tetracycline antibiotics (e.g., minocycline and doxycycline) because you may also be allergic to eravacycline.

Warnings and precautions

Talk to your doctor or nurse before you receive Xerava if you are concerned about any of the following:

Anaphylactic reactions
Anaphylactic (allergic) reactions have been reported with other tetracycline antibiotics. These can develop suddenly and can potentially be life-threatening. **Seek urgent medical attention** if you suspect you have an anaphylactic reaction whilst receiving Xerava. Symptoms to look out for include rash, swelling of the face, feeling lightheaded or faint, tightness of the chest, breathing difficulties, fast heartbeat, or losing consciousness (see also section 4).

Diarrhoea
Talk to your doctor or nurse if you are suffering from diarrhoea before being given Xerava. If you develop diarrhoea during or after your treatment, **tell your doctor straight away**. Do not take any medicine to treat your diarrhoea without first checking with your doctor (see also section 4).

Infusion site reactions
Xerava is given by an infusion (drip) directly into your vein. **Tell your doctor or nurse** if you notice any of the following at the site of infusion during or after your treatment: redness of the skin, rash, inflammation, or pain or tenderness.

New infection
Although Xerava fights certain bacteria, other bacteria and fungi may continue to grow. This is called 'overgrowth' or 'superinfection'. Your doctor will monitor you closely for any new infections or stop treatment with Xerava and give you another treatment if necessary.

Pancreatitis
Severe pain in the abdomen and back with fever may be signs of inflammation of the pancreas. Tell your doctor or nurse if you notice any of these side effects during your treatment with Xerava.

Liver problems
Talk to your doctor if you have liver problems or if you are overweight, particularly if you are also taking itraconazole (a medicine to treat fungal infections), ritonavir (a medicine used to treat viral infections) or clarithromycin (an antibiotic) as your doctor will monitor you for side effects.

Children and adolescents

This medicine should not be used in children under the age of 12 years or in adolescent weighing below 50 kg. Xerava must not be used in children below 8 years of age because it can cause permanent effects on their teeth such as discolouration.

Other medicines and Xerava

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines including rifampicin and clarithromycin (antibiotics), phenobarbital, carbamazepine and phenytoin (used to treat epilepsy), St. John's Wort (a herbal remedy used for treatment of depression and anxiety) itraconazole (a medicine to treat fungal infections), ritonavir, atazanavir, lopinavir and saquinavir (medicines used to treat viral infections), and cyclosporine (a medicine used to suppress the immune system).

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine. Xerava is not recommended for use during pregnancy as it can:

- permanently stain your unborn child's teeth
- delay the natural formation of the bones of your unborn child.

It is not known if Xerava passes into breast milk. Long-term use of other similar antibiotic medicines by breast-feeding mothers can stain the child's teeth permanently. Ask your doctor for advice before breast-feeding your baby.

Driving and using machines

Xerava may affect your ability to drive or use machines safely. Do not drive or use machines if you feel dizzy, light-headed or unsteady after receiving this medicine.

3. How you will be given Xerava

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

The recommended dose is based on body weight and is 1 mg/kg every 12 hours.

Your doctor may increase your dose (1.5 mg/kg every 12 hours) if you are taking other medicines including rifampicin, phenobarbital, carbamazepine, phenytoin, or St. John's Wort.

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

A course of treatment usually lasts for 4 to 14 days. Your doctor will decide how long you should be treated for.

If you are given more Xerava than you should

Xerava will be given to you in hospital by a doctor or nurse. It is, therefore, unlikely that you will be given too much. Tell your doctor or nurse immediately if you are concerned that you may have been given too much Xerava.

If you miss a dose of Xerava

Xerava will be given to you in hospital by a doctor or nurse. It is, therefore, unlikely that you will miss a dose. Tell your doctor or nurse immediately if you are concerned that you may have missed a dose.

4. Possible side effects

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

Seek urgent medical attention if you suspect you have an anaphylactic reaction, or develop any of the following symptoms, whilst receiving Xerava:

- Rash
- Swelling of the face
- Feeling lightheaded or faint
- Tightness of the chest
- Breathing difficulties
- Fast heartbeat
- Losing consciousness

Tell your doctor or nurse straightaway if you develop diarrhoea during or after your treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor.

Other side effects may include:

Common (may affect up to 1 in 10 people):

- Nausea
- Vomiting
- Inflammation and pain caused by blood clots at the injection site (thrombophlebitis)
- Inflammation of a vein causing pain and swelling (phlebitis)
- Redness or swelling at the site of the injection
- Low fibrinogen levels in the blood (a protein involved in blood clotting)
- Laboratory measurements of decreased ability to form blood clots

Uncommon (may affect up to 1 in 100 people):
- Diarrhoea
- Allergic reaction
- Inflammation of the pancreas which causes severe pain in the abdomen or back (pancreatitis)
- Rash
- Dizziness
- Headache
- Increased sweating
- Abnormal blood test results for liver

Tell your doctor or nurse if you have any of these side effects.

Other tetracycline antibiotics
Other side effects have been reported with other tetracycline antibiotics including minocycline and doxycycline. These include sensitivity to light, headaches, vision problems, or abnormal blood tests. Tell your doctor or nurse if you notice any of these during your treatment with Xerava.

Reporting of side effects

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

5. How to store Xerava

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

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

Store in a refrigerator (2 °C - 8° C). Keep the vial in the carton in order to protect from light.

Once the powder has been made into a solution and diluted ready for use, it should be given to you immediately. If not, it may be stored at room temperature and used within 12 hours.

Reconstituted Xerava should be a clear, pale yellow to orange solution. The solution should not be used if it appears to contain any particles or the solution is cloudy.

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

6. Contents of the pack and other information

What Xerava contains

- The active substance is eravacycline. Each vial contains 50 mg of eravacycline.
- The other ingredients are mannitol (E421), hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

What Xerava looks like and contents of the pack

Xerava is a pale yellow to dark yellow cake in a 10 mL glass vial. The powder for concentrate for solution for infusion (powder for concentrate) will be reconstituted in the vial with 5 mL of water for

injections. The reconstituted solution will be withdrawn from the vial and added to an infusion bag of sodium chloride 9 mg/mL (0.9%) solution for injection in the hospital.

Xerava is available in packs containing 1 vial or multipacks comprising 12 cartons, each containing 1 vial.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

Manufacturer

Patheon Italia S.p.A.
2° Trav. SX. Via Morolense, 5
03013 Ferentino (FR)
Italy

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

België/Belgique/Belgien Viatris Tél/Tel: + 32 (0)2 658 61 00	**Lietuva** PAION Pharma GmbH Tel: + 800 4453 4453
България PAION Pharma GmbH Тел.: + 800 4453 4453	**Luxembourg/Luxemburg** PAION Pharma GmbH Tél/Tel: + 800 4453 4453
Česká republika PAION Pharma GmbH Tel: + 800 4453 4453	**Magyarország** PAION Pharma GmbH Tel.: + 800 4453 4453
Danmark PAION Pharma GmbH Tlf: + 800 4453 4453	**Malta** PAION Pharma GmbH Tel: + 800 4453 4453
Deutschland PAION Pharma GmbH Tel: + 800 4453 4453	**Nederland** PAION Pharma GmbH Tel: + 800 4453 4453
Eesti PAION Pharma GmbH Tel: + 800 4453 4453	**Norge** PAION Pharma GmbH Tlf: + 800 4453 4453
Ελλάδα Viatris Hellas Ltd Τηλ: +30 210 0100002	**Österreich** PAION Pharma GmbH Tel: + 800 4453 4453
España Viatris Pharmaceuticals, S.L. Tel: + 34 900 102 712	**Polska** Viatris Healthcare Sp. z o.o. Tel.: + 48 22 546 64 00

France Viatris Santé Tél: +33 4 37 25 75 00	**Portugal** PAION Pharma GmbH Tel: + 800 4453 4453
Hrvatska PAION Pharma GmbH Tel: + 800 4453 4453	**România** BGP Products SRL Tel: +40 372 579 000
Ireland PAION Pharma GmbH Tel: + 800 4453 4453	**Slovenija** PAION Pharma GmbH Tel: + 800 4453 4453
Ísland PAION Pharma GmbH Sími: + 800 4453 4453	**Slovenská republika** PAION Pharma GmbH Tel: + 800 4453 4453
Italia Viatris Italia S.r.l. Tel: + 39 02 612 46921	**Suomi/Finland** PAION Pharma GmbH Puh/Tel: + 800 4453 4453
Κύπρος PAION Pharma GmbH Τηλ: + 800 4453 4453	**Sverige** PAION Pharma GmbH Tel: + 800 4453 4453
Latvija PAION Pharma GmbH Tel: + 800 4453 4453	

This leaflet was last revised in.

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

The following information is intended for healthcare professionals only:

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

Xerava must be reconstituted with water for injections and subsequently diluted using sodium chloride 9 mg/mL (0.9%) solution for injection.

Xerava must not be mixed with other medicinal products. If the same intravenous line is used for sequential infusion of different medicinal products, the line should be flushed before and after infusion with sodium chloride 9 mg/mL (0.9%) solution for injection.

The dose should be calculated based on the patient's weight; 1 mg/kg body weight.

Instructions for reconstitution

Aseptic technique must be followed when preparing the infusion solution. Each vial should be reconstituted with 5 mL water for injections, and swirled gently until the powder has dissolved entirely. Shaking or rapid movement should be avoided as it may cause foaming.

Reconstituted Xerava should be a clear, pale yellow to orange solution. The solution should not be used if particles are present or the solution is cloudy.

Preparation of the infusion 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. See example calculations in Table 1 (adults) and Table 2 (adolescents 12 - 17 years weighing at least 50 kg).

Gently invert the bag to mix the solution.

Table 1 Example calculations for adult patients weighing 40 kg to 200 kg[1]

Patient weight (kg)	**Total Dose (mg)**	**Number of vials to reconstitute**	**Total volume to be diluted (mL)**	**Recommended infusion bag size (mL)**
40	40	1	4	100
60	60	2	6	250
80	80	2	8	250
100	100	2	10	250
150	150	3	15	500
200	200	4	20	500

[1] The exact dose needs to be calculated based on the specific patient weight.

For adult patients weighing **≥ 40 kg – < 50 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 100 mL infusion bag.

For adult patients weighing **50 kg – 100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

For adult patients weighing >**100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 500 mL infusion bag.

Table 2 Example calculations for adolescent patients (12 - 17 years) weighing 50 kg to 90 kg[1]

Patient weight (kg)	Total dose (mg)	Number of vials to reconstitute	Total volume to be diluted (mL)	Recommended infusion bag size (mL)
50	50	1	5	250
60	60	2	6	250
70	70	2	7	250
80	80	2	8	250
90	90	2	9	250

[1] The exact dose needs to be calculated based on the specific patient weight.

For adolescent patients weighing **50 kg – 90 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

Infusion

The infusion solution should be inspected visually for particulate matter prior to administration. Reconstituted and diluted solutions containing visible particles or that are cloudy in appearance should be discarded.

Following dilution, Xerava is administered intravenously over approximately 1 hour. The recommended dose regimen of Xerava is 1 mg/kg every 12 hours for 4 to 14 days.

The reconstituted and diluted solution must be administered as an intravenous infusion only. It must not be administered as an intravenous bolus.

For single use only, any unused solution should be discarded.

Package leaflet: Information for the patient

Xerava 100 mg powder for concentrate for solution for infusion
eravacycline

Read all of this leaflet carefully before you receive this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

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

1. What Xerava is and what it is used for

What Xerava is

Xerava is an antibiotic medicine that contains the active substance eravacycline. It belongs to a group of antibiotics called 'tetracyclines' which work by stopping the growth of certain infectious bacteria.

What Xerava is used for

Xerava is used to treat adolescents from the age of 12 years weighing at least 50 kg, and adults, with a complicated infection in the abdomen.

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

You must not receive Xerava

- if you are allergic to eravacycline or any of the other ingredients of this medicine (listed in section 6).
- if you are allergic to any tetracycline antibiotics (e.g., minocycline and doxycycline) because you may also be allergic to eravacycline.

Warnings and precautions

Talk to your doctor or nurse before you receive Xerava if you are concerned about any of the following:

Anaphylactic reactions
Anaphylactic (allergic) reactions have been reported with other tetracycline antibiotics. These can develop suddenly and can potentially be life-threatening. **Seek urgent medical attention** if you suspect you have an anaphylactic reaction whilst receiving Xerava. Symptoms to look out for include rash, swelling of the face, feeling lightheaded or faint, tightness of the chest, breathing difficulties, fast heartbeat, or losing consciousness (see also section 4).

Diarrhoea
Talk to your doctor or nurse if you are suffering from diarrhoea before being given Xerava. If you develop diarrhoea during or after your treatment, **tell your doctor straight away**. Do not take any medicine to treat your diarrhoea without first checking with your doctor (see also section 4).

Infusion site reactions
Xerava is given by an infusion (drip) directly into your vein. **Tell your doctor or nurse** if you notice any of the following at the site of infusion during or after your treatment: redness of the skin, rash, inflammation, or pain or tenderness.

New infection
Although Xerava fights certain bacteria, other bacteria and fungi may continue to grow. This is called 'overgrowth' or 'superinfection'. Your doctor will monitor you closely for any new infections or stop treatment with Xerava and give you another treatment if necessary.

Pancreatitis
Severe pain in the abdomen and back with fever may be signs of inflammation of the pancreas. Tell your doctor or nurse if you notice any of these side effects during your treatment with Xerava.

Liver problems
Talk to your doctor if you have liver problems or if you are overweight, particularly if you are also taking itraconazole (a medicine to treat fungal infections), ritonavir (a medicine used to treat viral infections) or clarithromycin (an antibiotic) as your doctor will monitor you for side effects.

Children and adolescents

This medicine should not be used in children under the age of 12 years or in adolescent weighing below 50 kg. Xerava must not be used in children below 8 years of age because it can cause permanent effects on their teeth such as discolouration.

Other medicines and Xerava

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines including rifampicin and clarithromycin (antibiotics), phenobarbital, carbamazepine and phenytoin (used to treat epilepsy), St. John's Wort (a herbal remedy used for treatment of depression and anxiety) itraconazole (a medicine to treat fungal infections), ritonavir, atazanavir, lopinavir and saquinavir (medicines used to treat viral infections), and cyclosporine (a medicine used to suppress the immune system).

Pregnancy and breast-feeding

If you are pregnant or breast-feeding,, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine. Xerava is not recommended for use during pregnancy as it can:

- permanently stain your unborn child's teeth
- delay the natural formation of the bones of your unborn child.

It is not known if Xerava passes into breast milk. Long-term use of other similar antibiotic medicines by breast-feeding mothers can stain the child's teeth permanently. Ask your doctor for advice before breast-feeding your baby.

Driving and using machines

Xerava may affect your ability to drive or use machines safely. Do not drive or use machines if you feel dizzy, light-headed or unsteady after receiving this medicine.

3. How you will be given Xerava

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

The recommended dose is based on body weight and is 1 mg/kg every 12 hours.

Your doctor may increase your dose (1.5 mg/kg every 12 hours) if you are taking other medicines including rifampicin, phenobarbital, carbamazepine, phenytoin, or St. John's Wort.

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

A course of treatment usually lasts for 4 to 14 days. Your doctor will decide how long you should be treated for.

If you are given more Xerava than you should

Xerava will be given to you in hospital by a doctor or nurse. It is, therefore, unlikely that you will be given too much. Tell your doctor or nurse immediately if you are concerned that you may have been given too much Xerava.

If you miss a dose of Xerava

Xerava will be given to you in hospital by a doctor or nurse. It is, therefore, unlikely that you will miss a dose. Tell your doctor or nurse immediately if you are concerned that you may have missed a dose.

4. Possible side effects

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

Seek urgent medical attention if you suspect you have an anaphylactic reaction, or develop any of the following symptoms, whilst receiving Xerava:

- Rash
- Swelling of the face
- Feeling lightheaded or faint
- Tightness of the chest
- Breathing difficulties
- Fast heartbeat
- Losing consciousness

Tell your doctor or nurse straightaway if you develop diarrhoea during or after your treatment. Do not take any medicine to treat your diarrhoea without first checking with your doctor.

Other side effects may include:

Common (may affect up to 1 in 10 people):

- Nausea
- Vomiting
- Inflammation and pain caused by blood clots at the injection site (thrombophlebitis)
- Inflammation of a vein causing pain and swelling (phlebitis)
- Redness or swelling at the site of the injection
- Low fibrinogen levels in the blood (a protein involved in blood clotting)
- Laboratory measurements of decreased ability to form blood clots

Uncommon (may affect up to 1 in 100 people):
- Diarrhoea
- Allergic reaction
- Inflammation of the pancreas which causes severe pain in the abdomen or back (pancreatitis)
- Rash
- Dizziness
- Headache
- Increased sweating
- Abnormal blood test results for liver

Tell your doctor or nurse if you have any of these side effects.

Other tetracycline antibiotics
Other side effects have been reported with other tetracycline antibiotics including minocycline and doxycycline. These include sensitivity to light, headaches, vision problems, or abnormal blood tests. Tell your doctor or nurse if you notice any of these during your treatment with Xerava.

Reporting of side effects

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

5. How to store Xerava

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

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

Store in a refrigerator (2 °C – 8 °C). Keep the vial in the carton in order to protect from light.

Once the powder has been made into a solution and diluted ready for use, it should be given to you immediately. If not, it may be stored at room temperature and used within 12 hours.

Reconstituted Xerava should be a clear, pale yellow to orange solution. The solution should not be used if it appears to contain any particles or the solution is cloudy.

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

6. Contents of the pack and other information

What Xerava contains

- The active substance is eravacycline. Each vial contains 100 mg of eravacycline.
- The other ingredients are mannitol (E421), hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

What Xerava looks like and contents of the pack

Xerava is a pale yellow to dark yellow cake in a 10 mL glass vial. The powder for concentrate for solution for infusion (powder for concentrate) will be reconstituted in the vial with 5 mL of water for injections or with 5 mL sodium chloride 9 mg/mL (0.9%) solution for injection. The reconstituted

solution will be withdrawn from the vial and added to an infusion bag of sodium chloride 9 mg/mL (0.9%) solution for injection in the hospital.

Xerava is available in packs containing 1 vial, 10 vials or multipacks comprising 12 cartons, each containing 1 vial.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Germany

Manufacturer

PAION Pharma GmbH
Heussstraße 25
52078 Aachen
Germany

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

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

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The following information is intended for healthcare professionals only:

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

Xerava must be reconstituted with water for injections or with sodium chloride 9 mg/mL (0.9%) solution for injection, and subsequently diluted using sodium chloride 9 mg/mL (0.9%) solution for injection.

Xerava must not be mixed with other medicinal products. If the same intravenous line is used for sequential infusion of different medicinal products, the line should be flushed before and after infusion with sodium chloride 9 mg/mL (0.9%) solution for injection.

The dose should be calculated based on the patient's weight; 1 mg/kg body weight.

Instructions for reconstitution

Aseptic technique must be followed when preparing the infusion solution. Each vial should be reconstituted with 5 mL water for injections or with 5 mL sodium chloride 9 mg/mL (0.9%) solution for injection, and swirled gently until the powder has dissolved entirely. Shaking or rapid movement should be avoided as it may cause foaming.

Reconstituted Xerava should be a clear, pale yellow to orange solution. The solution should not be used if particles are present or the solution is cloudy.

Preparation of the infusion 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. See example calculations in Table 1 (adults) and Table 2 (adolescents 12 - 17 years weighing at least 50 kg).

Gently invert the bag to mix the solution.

Table 1 Example calculations for adult patients weighing 40 kg to 200 kg[1]

Patient weight (kg)	**Total Dose (mg)**	**Number of vials to reconstitute**	**Total volume to be diluted (mL)**	**Recommended infusion bag size (mL)**
40	40	1	2	100
60	60	1	3	250
80	80	1	4	250
100	100	1	5	250
150	150	2	7.5	500
200	200	2	10	500

[1] The exact dose needs to be calculated based on the specific patient weight.

For adult patients weighing **≥ 40 kg – < 50 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 100 mL infusion bag.

For adult patients weighing **50 kg – 100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

For adult patients weighing >**100 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 500 mL infusion bag.

Table 2 Example calculations for adolescent patients (12 - 17 years) weighing 50 kg to 90 kg[1]

Patient weight (kg)	Total dose (mg)	Number of vials to reconstitute	Total volume to be diluted (mL)	Recommended infusion bag size (mL)
50	50	1	2.5	250
60	60	1	3	250
70	70	1	3.5	250
80	80	1	4	250
90	90	1	4.5	250

[1] The exact dose needs to be calculated based on the specific patient weight.

For adolescent patients weighing **50 kg – 90 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 250 mL infusion bag.

Infusion

The infusion solution should be inspected visually for particulate matter prior to administration. Reconstituted and diluted solutions containing visible particles or that are cloudy in appearance should be discarded.

Following dilution, Xerava is administered intravenously over approximately 1 hour. The recommended dose regimen of Xerava is 1 mg/kg every 12 hours for 4 to 14 days.

The reconstituted and diluted solution must be administered as an intravenous infusion only. It must not be administered as an intravenous bolus.

For single use only, any unused solution should be discarded.