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 for the treatment of complicated intra-abdominal infections (cIAI) in adults (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 and adolescents less than 18 years of age have not been established. No data are available. Xerava should not be used in children aged under 8 years because of teeth 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 sections 4.2 and 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 reactions[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.

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 Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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

Table 2 Minimum inhibitory concentration breakpoints of eravacycline for different pathogens

Pathogen	**MIC Breakpoints (µg/mL)**	
	Susceptible (S ≤)	**Resistant (R >)**
Escherichia coli	0.5	0.5
Staphylococcus aureus	0.25	0.25
Enterococcus spp.	0.125	0.125
Viridans *Streptococcus spp.*	0.125	0.125

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 3.

Table 3 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.

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

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 4.

Gently invert the bag to mix the solution.

Table 4Example calculations for weights ranging from 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
40	40	1	4	100 mL
60	60	2	6	250 mL
80	80	2	8	250 mL
100	100	2	10	250 mL
150	150	3	15	500 mL
200	200	4	20	500 mL

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

For patients weighing ≥ **40 kg – 49 kg**:
Calculate the required volume of the reconstituted solution based on the patient's weight and inject into a 100 mL infusion bag.

For 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 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.

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

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52078 Aachen

Germany

8 MARKETING AUTHORISATION NUMBER(S)

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