SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TIRONEM
Powder for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:
Doripenem Monohydrate
Equivalent to Doripenem……500 mg.

The medicinal product does not contain any excipients.

3. PHARMACEUTICAL FORM

Powder for infusion
A white to slightly yellowish, off-white crystalline powder

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

TIRONEM is indicated for the treatment of the following infections in adults:
- Nosocomial pneumonia (including ventilator-associated pneumonia).
- Complicated intra-abdominal infections

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

4.2 Posology And Method of Administration

The recommended dosage and administration by infection are shown in the following table:

Infection	Dosage	Frequency	Infusion Time
Nosocomial pneumonia (including ventilator-associated pneumonia)	500 mg	Every 8 hours	1 or 4 hours*
Complicated intra-abdominal infection	500 mg	Every 8 hours	1 hours

*Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable for infection with less susceptible pathogens. This dosing regimen should also be considered in particularly severe infections.

The usual treatment duration of **TIRONEM** therapy is 5-14 days, depending on the patient's clinical response. **TIRONEM** was given for up to 14 days in clinical studies, and the safety of longer durations of therapy has not been established. After commencing

treatment with intravenous **TIRONEM**, a switch to appropriate oral therapy to complete the treatment course is possible once clinical improvement has been established.

Dosage in pediatric patients
TIRONEM is not recommended for use in children below 18 years of age due to a lack of safety and efficacy data.

Dosage in patients with impaired renal function
In patients with mild renal impairment (i.e., creatinine clearance (CrCl) is 51-79 mL/min). The dosage of TIRONEM should be 250 mg every 8 hours.
In patients with moderate renal impairment (CrCl ≥ 30 to ≤ 50 ml/min), the dose of doripenem should be 250 mg every 8 hours.
In patients with severe renal impairment (CrCl < 30 mL/min), the dosage of **TIRONEM** should be 250 mg every 12 hours. In patients prescribed 1 g every 8 hours as a 4-hour infusion, the dose should be similarly adjusted (moderate renal impairment: 500 mg every 8 hours; severe renal impairment: 500 mg every 12 hours)

Due to limited clinical data and an expected increased exposure of TIRONEM and its metabolite (doripenem-M-1), **TIRONEM** should be used with caution in patients with severe renal impairment.

Dosage in patients on dialysis
TIRONEM is hemodialyzable; Doripenem dosing and administration recommendations for patients on continuous renal replacement therapies are shown in the following table.

CRRT procedure	Glomerular filtration rate	Dose	Frequency	Infusion time [a, b]	Target attainment (MIC)
CVVH	≤ 30 ml/min	250 mg	every 12 hours	4 hours	≤ 1 mg/l
CVVHDF	< 5 ml/min	250 mg	every 12 hours	4 hours	≤ 1 mg/l
CVVHDF	5-30 ml/min	500 mg	every 12 hours	4 hours	≤ 1 mg/l

CRRT: continuous renal replacement therapy; CVVH: continuous venovenous haemofiltration; CVVHDF: continuous venovenous haemodiafiltration; MIC: minimum inhibitory concentration

[a] For patients with acute renal insufficiency on CRRT, an infusion time of 4 hours is required, taking into consideration the possible increases in non-renal clearance of carbapenems in patients with acute renal insufficiency.

[b] Patients with chronic renal impairment on CRRT can be treated with either a 1 or 4-hour infusion time. Based mainly on PK/PD considerations, a 4-hour infusion time may be more suitable to maximize the percentage time during the dosing interval that the plasma concentration of doripenem exceeds the minimum inhibitory concentration (%T > MIC), (see section 5.1).

Dosing recommendations for pathogens with MIC > 1 mg/l have not been established for continuous renal replacement therapy due to the potential for accumulation of doripenem and doripenem-M-1 metabolite. Close safety monitoring is advised for patients on continuous renal replacement therapy, due to limited clinical data and an expected increased exposure to doripenem-M-1 metabolite

Dosage in elderly patients (> 65 years of age)
Dosage adjustment is necessary in elderly patients, except in cases of moderate to severe renal insufficiency (see Dosage in patients with impaired renal function above)

Dosage in patients with impaired hepatic function
No dose adjustment is necessary.

Method of Administration
TIRONEM is to be reconstituted and then further diluted prior to administration by intravenous infusion over a period of one or four hours.

4.3 Contraindications

- Hypersensitivity to the active substance
- Hypersensitivity to any other carbapenem antibacterial agent.
- Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of betalactam antibacterial agent (e.g. Penicillins or Cephalosporins).

4.4 Special warnings and precautions for use

General
The selection of doripenem to treat an individual patient should take into account the appropriateness of using a carbapenem antibacterial agent based on factors such as severity of the infection, the prevalence of resistance to other suitable antibacterial agents and the risk of selecting for carbapenem-resistant bacteria.
Caution on the choice of antibiotic agent and dose should be taken when treating patients with late-onset ventilator-associated pneumonia (> 5 days hospitalisation) and in other nosocomial pneumonia cases where pathogens with decreased susceptibility are suspected or confirmed, such as *Pseudomonas* spp. and *Acinetobacter* spp.
Concomitant use of an aminoglycoside may be indicated when *Pseudomonas aeruginosa* infections are suspected or proven to be involved in the approved indications.

Hypersensitivity reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have occurred in patients receiving beta-lactam antibiotics. Before therapy with Doripenem is started, careful inquiry should be made concerning a previous history of hypersensitivity reactions to

other active substances in this class or to beta-lactam antibiotics. Doripenem should be used with caution in patients with such a history. Should a hypersensitivity reaction to doripenem occur, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reactions require immediate emergency treatment.

Seizures
Seizures have been reported during treatment with carbapenems, including doripenem (see section 4.8). Seizures in clinical trials with doripenem occurred most commonly in those with pre-existing central nervous system (CNS) disorders (e.g. stroke or history of seizures), compromised renal function and at doses greater than 500 mg.

Pseudomonas
Pseudomembranous colitis due to *Clostridium difficile* has been reported with Doripenem and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of Doripenem.

Overgrowth of non-susceptible bacteria
Administration of doripenem, like other antibiotics, has been associated with emergence and selection of strains with reduced susceptibility. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken. Prolonged use of Doripenem should be avoided.

Drug interaction with valproic acid
The concomitant use of doripenem and valproic acid/sodium valproate is not recommended.

Pneumonitis with inhalational use
When doripenem was used investigationally via inhalation, pneumonitis occurred. Therefore, doripenem should not be administered by this route.

Continuous renal replacement therapy
The exposure to the metabolite doripenem-M-1 in patients on continuous renal replacement therapy may be increased to levels where no *in vivo* safety data are presently available. The metabolite lacks target pharmacological activity but other possible pharmacological effects are unknown. Therefore, close safety monitoring is advised.

Adverse drug reactions that led to **TIRONEM** discontinuation were nausea, diarrhea, puritus, vulvomycotic infection, hepatic enzyme increased and rash. The most common adverse reactions were headache diarrhea and nausea.

Infections and infestation	Oral candidiasis, vulvomycotic infection
Immune system disorders	Hypersensitivity reactions (see section Warning and Precautions)
Nervous system disorders	Headache
Vascular disorders	Common: phlebitis
Gastrointestinal disorders	Nausea, diarrhea, colitis cause by *C.*
	Difficile (see section Warning and Precautions)
Hepato-biliary disorders	Hepatic enzyme increased
Skin and subcutaneous tissue disorders	Pruritus, rash

4.5 Special warnings and precautions for use

Hypersensitivity Reactions
Serious and occasionally fatal hypersensitivity reactions (anaphylactic) have occurred in patient receiving betalactam antibiotics. Before therapy with **TIRONEM** is started, careful inquiry should be made concerning a previous history of hypersensitivity reactions to other active substances in this class or to betalactam antibiotics. **TIRONEM** should be used with caution in patients with such a history. If a hypersensitivity reaction to **TIRONEM** occur, it should be discontinued immediately and appropriate measures taken. Serious acute hypersensitivity (anaphylactic) reaction require immediate emergency treatment.

Seizures
Although infrequently, seizure have been reported during treatment with other Carbapenems.

Pseudomembranous colitis
Just like the use of any antibacterial drugs, Pseudomembranous colitis due to Clostridium difficile has been reported with **TIRONEM** as with nearly all antibacterial agents and may range in severity from mild to life-treatening. Therefore, it is important to consider this diagnosis in patient who present with diarrhea during or subsequent to the administration of Doripenem (see section Adverse Reactions).

Super-infection
Administration of **TIRONEM**, like other antibiotics, has been associated with emergence and selection of strains with reduced susceptibility. Patients should be carefully monitored during therapy. If super-infection occurs, appropriate measures should be taken. Prolonged use of **TIRONEM** should be avoided.

Pneumonitis
Pneumonitis can occur if **TIRONEM** used via inhalation. Therefore, **TIRONEM** should not be administered by this route.

4.6 Interaction with Other Medicinal Products and Other Forms of Interactions

TIRONEM undergoes little to no Cytochrome P450 (CYP450) mediated metabolism. Based on in vitro studies it is not expected that TIRONEM will inhibit or induce the activities of CYP450. Therefore, no CYP450 related drug interactions are to be expected.

- Carbapenem antibacterial agents may reduce serum Valproic Acid concentrations. Serum concentrations of Valproic Acid should be mmonitored if TIRONEM is administered concomitantly with Valproic Acid.
- Probenecid competes with TIRONEM for renal tubular secretion an reduces the renal clearance of TIRONEM. In an interaction study, the mean doripenem AUC increased by 75% following co-administration with Probenecid. Therefore, co-administration of Probenecid TIRONEM is not recommended. An interaction with other drugs eliminated by renal tubular secretion cannot be excluded.

4.7 Pregnancy and Lactation

Pregnancy

Clinical data of **TIRONEM** on pregnancy are very limited. Animal studie sare insufficient to draw conclusion for pregnancy, embryonal/foetal development, porturition or postnatal development. The potential risk for human is unknown. **TIRONEM** should not be used during pregnancy unless clearly necessary.

Lactation

It is not known whether **TIRONEM** is excreted in human breast milk. A study in rats has shown that **TIRONEM** and its metabolite are transferred to milk. A decision on whether to continue/discontinue breastfeeding or to continue/discontinue therapy with **TIRONEM** should be made taking into account the benefit of breastfeeding to the child and the benefit of **TIRONEM** therapy to the woman.

4.8 Effect on Ability to Drive and Use Machine

No studies on the effects of **TIRONEM** on the ability to drive and use machines have been performed. Based on reported adverse drug reaction, it is not anticipated that **TIRONEM** will affect the ability to drive and use machines.

4.9 Overdose

No case of overdose has been reported. In the event of overdose, **TIRONEM** should be discontinued and general supportive treatment given until renal elimination takes place. **TIRONEM** can be removed by haemodialysis; however, no information is available on the use of haemodialysis to treat overdose by **TIRONEM.**

5. PHARMACOLOGICAL PROPERTIES

5.1 Phamacodynamic properties

Pharmacotherapeutic group: Carbapenems

ATC Code : J01DH04

Mecanisms of Action:

Doripenem is synthetic Carbapenems antibacterial agent.Doripenem exerts its bactericidal activity by inhibiting bacterial cell wall biosynthesis. Doripenem inactivates multiple essential Penicillin-Binding Proteins (PBPs) resulting in inhibition of cell wall synthesis with subsequent cell death.

In vitro Doripenem showed tittle potential to antagonize or be antagonized by other antibacterial agents.

Additive activity or weak synergy with Amikacin and Levofloxacin has been seen for *Pseudmonas aeruginosa* and for gram-positive bacteria with Daptomycin, Linezolid, Levofloxacin, and Vancomycin.

Mecanisms of Resistance:

Bacterial resistance mechanisms that effect Doripenem include active substance inactivation by Carbapenem hydrolyzing enzymes, mutants or acquired PBP's, decreased outer membrane permeability and active efflux. Doripenem is stable to hydrolysis by most *beta-lactamase*, including *Penicillinases* and *Cephalosporinases* produced by gram positive and gram negative bacteria, with the exception of relatively rare carbapenem hydrolyzing beta-lactamases. Species resistant to other Carbapenems do generally express coresistance to Doripenem. *Methicillin-resistant Staphylococci* should always be considered as resistant to Doripenem. As with other antimicrobial agents, including Carbapenems, Doripenem has been shown to select for resistant bacterial strains.

Breakpoints :

Minimum Inhibitory Concentration (MIC) breakpoints established by the European Committee of Antimicrobial Susceptibility Testing (EUCAST) are as follows:

Non species related	S ≤ 1 mg/L and R > 4 mg/L
Staphylococci	Inferred from the Methicillin breakpoint
Enterobactericeae	S ≤ 1 mg/L and R > 4 mg/L
Acinetobacter spp.	S ≤ 1 mg/L and R > 4 mg/L
Pseudomonas spp.	S ≤ 1 mg/L and R > 4 mg/L
Streptococcus spp. other than *S. Pneumonia*	S ≤ 1 mg/L and R > 1 mg/L

S. Pneumonia	S ≤ 1 mg/L and R > 1 mg/L
Enterococci	"inappropriate target"
Haemophilus spp.	S ≤ 1 mg/L and R > 1 mg/L
N. Gonorrhoeae	IE (insufficient evidence)
Anaerobes	S ≤ 1 mg/L and R > 1 mg/L

Susceptibility :

The prevalence of acquired resistance vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Localise clusters of infection due to Carbapenem resistant have been reported in the European Union. The information below gives only approximate guidance on the probability as to whether the micro organism will be susceptible to Doripenem or not.

Commonly Susceptible Species

Gram positive Aerobes:

Enterococcus faecalis[*s]
Staphylococcus aureus (Methicillin susceptible strains only)[*^]
Staphylococcus spp. (Methicillin susceptible strains only)[*^]
Streptococcus pneumoniae[*]
Streptococcus spp.

Gram-negative aerobes:

Citrobacter citrobacter freundii
Enterobacter aerogenes
Haemophilus influenzae[*]
Escherichia coli
Klebsiella pneumoniae[*]
Klebsiella oxytoca
Morganella morganii
Proteus vulgaris
Providencia rettgeri
Providencia stuartii
Salmonella species
Serratia marcescens
Shigella species

Anaerobes:

Bacteroides fragilis[*]
Bacteroides caccae[*]
Bacteroides avatus[*]
Bacteroides uniformis[*]
Bacteroides thetaiotaomicron[*]
Bacteriodes vulgatus[*]
Bilophila wadsworthia

Peptostreptococcus magnus
Peptostreptococcus micros[*]
Porphyromonas spp.
Provotella spp.
Sutterella wadsworthenis

Species for which acquired resistance may be a problem:
Acinetobacter baumanii[*]
Acinetobacter spp.
Burkholderia cepacias[+]
Pseudomonas aeruginosa[+]

Inherently resistant organisms:
Gram-positive aerobes
Enterococcus faecium

Gram-negative aerobes:
Stenotrophomonas malthopilia
Legionella spp.

[*] species against which activity has been demonstrated in clinical studies
[s] species that show natural intermediate susceptibility
[+] species with > 50% acquired resistance in one or more Member States
[^] all Methicillin-resistant Staphylococci should be regarded as resistant to Doripenem

5.2 Pharmacokinetic properties

The mean C_{max} and $AUC_{0-\infty}$ of doripenem in healthy subjects across studies following administration of 500 mg over 1 hour are approximately 23 µg/mL and 36 µg.h/mL, respectively. The mean C_{max} and $AUC_{0-\infty}$ of doripenem in healthy subjects across studies following administration of 500 mg and 1 g over 4 hours are approximately 8 µg/mL and 17 µg/mL, and 34 µg.h/mL and 68 µg.h/mL, respectively. There is no accumulation of doripenem following multiple intravenous infusions of either 500 mg or 1 g administered every 8 hours for 7 to 10 days in patients with normal renal function.

Distribution
The average binding of doripenem to plasma proteins was approximately 8.1% and is independent of plasma concentrations. The volume of distribution at steady state is approximately 16.8 L, similar to extracellular fluid volume in man. Doripenem penetrates well into several body fluids and tissues, such as uterine tissue, retroperitoneal fluid, prostatic tissue, gallbladder tissue, and urine.

Metabolism
Metabolism of doripenem to a microbiologically inactive ring-opened metabolite occurs primarily via dehydropeptidase-I. Doripenem undergoes little to no Cytochrome P450 (CYP450) mediated

metabolism. *In vitro* studies have determined that doripenem does not inhibit or induce the activities of CYP isoforms 1A2, 2A6, 2C9, 2C19, 2D6, 2E1 or 3A4.

Elimination

Doripenem is primarily eliminated unchanged by the kidneys. Mean plasma terminal elimination halflife of doripenem in healthy young adults is approximately 1 hour and plasma clearance is approximately 15.9 l/hour. Mean renal clearance is 10.3 l/hour. The magnitude of this value, coupled with the significant decrease in the elimination of doripenem seen with concomitant probenecid administration, suggests that doripenem undergoes glomerular filtration, tubular secretion and reabsorption. In healthy young adults given a single 500 mg dose of Doripenem, 71% and 15% of the dose was recovered in urine as unchanged active substance and ring-opened metabolite, respectively.

Following the administration of a single 500 mg dose of radiolabeled doripenem to healthy young adults, less than 1% of the total radioactivity was recovered in faeces. The pharmacokinetics of doripenem are linear over a dose range of 500 mg to 1 g when intravenously infused over either 1 or 4 hours.

Renal insufficiency

Following a single 500 mg dose of Doripenem, doripenem AUC increased 1.6-fold, 2.8-fold, and 5.1-fold in subjects with mild (CrCl 51-79 mL/min), moderate (CrCl 31-50 mL/min), and severe renal impairment (CrCl ≤ 30 mL/min), respectively, compared to age-matched healthy subjects with normal renal function (CrCl >80 mL/min). AUC of the microbiologically inactive ring-opened metabolite is expected to be considerably increased in patients with severe renal impairment compared with healthy subjects. Dosage adjustment is necessary in patients with moderate and severe renal impairment (see section 4.2).

AUCs of doripenem and of the microbiologically inactive ring-opened metabolite are substantially increased in patients who require haemodialysis compared with healthy subjects. In a study where six subjects with end stage renal disease on haemodialysis received a single dose of 500 mg doripenem by i.v. infusion, the amount of doripenem removed during the four-hour haemodialysis session was 231 mg (46% of the dose).

Hepatic impairment

The pharmacokinetics of doripenem in patients with hepatic impairment have notbeen established. As doripenem does not appear to undergo hepatic metabolism, the pharmacokinetics of Doripenem are not expected to be affected by hepatic impairment.

Elderly

The impact of age on the pharmacokinetics of doripenem was evaluated in healthy elderly male and female subjects (66-84 years of

age). Doripenem AUC increased 49% in elderly adults relative to young adults. These changes were mainly attributed to age-related changes in renal function. No dosage adjustment is necessary in elderly patients, except in cases of moderate to severe renal insufficiency (see section 4.2).

Gender
The effect of gender on the pharmacokinetics of doripenem was evaluated in healthy male and female subjects. Doripenem AUC was 15% higher in females compared to males. No dose adjustment is recommended based on gender.

Race
The effect of race on doripenem pharmacokinetics was examined through a population pharmacokinetic analysis. No significant difference in mean doripenem clearance was observed across race groups and therefore, no dosage adjustment is recommended for race.

5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and genotoxicity. However, because of the design of the repeat dose toxicity studies and differences in pharmacokinetics in animals and humans, continuous exposure of animals was not assured in these studies.

No reproductive toxicity was observed in studies performed in rats and rabbits. However, these studies are of limited relevance because studies were performed with single daily dosing resulting in less than one tenth of daily doripenem exposure duration in animals.

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
None.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.3.

6.3 Shelf life
24 months

Storage of reconstituted solutions: Upon reconstitution with sterile water for injections or sodium chloride 9 mg/ml (0.9%) solution for injection, Doripenem suspension in the vial may be held for up to 1 hour below 30°C prior to transfer and dilution in the infusion bag.
Following dilution in the infusion bag with sodium chloride 9 mg/ml (0.9%) solution for injection or dextrose 50 mg/ml (5%) solution for injection, Doripenem infusions stored at controlled room temperature or under refrigeration should be completed according to the times in the following table:

Time by which reconstitution, dilution and infusion must complete for **TIRONEM**

Infusion solution	Solution stored at room temperature	Solution stored in a refrigerator (2°C-8°C)
Sodium chloride 9 mg/mL (0.9%) solution for injection	12 hours	72 hours*
*dextrose 50 mg/mL (5%) solution for injection	4 hours	24 hours*

* Once removed from the refrigerator, infusions should be completed within the room temperature stability time, provided the total refrigeration time, time to reach room temperature and infusion time does not exceed refrigeration stability time.

+ Dextrose 50 mg/ml (5%) solution for injection should not be used for infusion durations greater than 1 hour.

Chemical and physical in-use stability has been demonstrated for the times and solutions shown in the above table.

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 24 hours at 2°C-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special Precaution for Storage

This medicinal product does not require any special storage conditions.
For storage conditions of the reconstituted medicinal product, and infusion solutions see section 6.3.

6.5 Nature and Contents of Containers

Box of 1 vial @ 500 mg

6.6 Special Precautions for Disposal and other Handling

Each vial is for single use only.

TIRONEM is reconstituted and then further diluted prior to infusion.

Preparation of 500 mg dose of solution for infusion

1. Add 10 mL of sterile water for injections orsodium chloride 9 mg/mL (0.9%) solution for injection to the vial and shake it to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection and mix to complete dissolution. Infuse all of

this solution to administer a 500 mg dose of doripenem.

Preparation of 250 mg dose of solution for infusion for patients with moderate or severe renal impairment

1. Add 10 mL of sterile water for injections orsodium chloride 9 mg/mL (0.9%) solution for injection to the vial and shake it to form a suspension.
2. Inspect the suspension visually for foreign matter. Note: the suspension is not for direct infusion.
3. Withdraw the suspension using a syringe and needle and add it to an infusion bag containing 100 mL of either sodium chloride 9 mg/mL (0.9%) solution for injection or dextrose 50 mg/mL (5%) solution for injection and mix to complete dissolution. Remove 55 mL of this solution from the infusion bag and discard. Infuse all of the remaining solution to administer a 250 mg dose of Doripenem.

TIRONEM solutions for infusion range from clear, colourless solutions to solutions that are clear and slightly yellow. Variations in colour within this range do not affect the potency of the product.

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

7. MARKETING AUTHORIZATION HOLDER

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8. Marketing authorization number(s)

H2025/CTD9804/21319.

9. Date of first authorization/renewal of the authorization

8th October 2025.

10. Date of revision of the text

8th October 2025.