SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zavicefta 2g/0.5g powder for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftazidime (as pentahydrate) equivalent to 2 g and avibactam (as sodium salt) equivalent to 0.5 g.

After reconstitution, 1 ml of solution contains 167.3 mg of ceftazidime and 41.8 mg of avibactam (See section 6.6).

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

A white to yellow sterile powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zavicefta is indicated in adults for the treatment of the following infections (see sections 4.4 and 5.1):

- Complicated Intra-Abdominal Infection (cIAI)
- Complicated Urinary Tract Infection, including Pyelonephritis (cUTI)
- Hospital-acquired Pneumonia (HAP), including ventilator associated pneumonia (VAP)
- Infections due to aerobic Gram-negative organisms in patients with limited treatment options

Consideration should be given to official guidance on the appropriate use of antibacterial agents. For treatment of cIAI use in combination with metronidazole.

4.2 Posology and method of administration

The recommended dosage of Zavicefta is 1 vial where each vial contains 2 g ceftazidime and 0.5 g avibactam administered by intravenous (IV) infusion in a volume of 100 ml at a constant rate over 120 minutes in patients aged 18 years or older. Treatment is repeated every 8 hours. For patients with renal impairment where CrCl≤50 ml/min, see dose recommendations in Table 2.

Treatment duration

Table 1 Summary of the treatment duration by indication or condition

Indication	Treatment Duration
Complicated Intra-Abdominal Infection (cIAI)	5-14 days
Complicated Urinary Tract Infection (cUTI), including Pyelonephritis	5-10 days[1]

Hospital-acquired Pneumonia, including ventilator associated pneumonia	7-14 days
Infections due to aerobic Gram-negative organisms in patients with limited treatment options	Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress

[1]Treatment duration includes intravenous plus oral treatment. The time to switch from intravenous Zavicefta to oral treatment with another antibiotic depends on the clinical situation, but is normally after about 5 days (the minimum duration of treatment with ceftazidime-avibactam in clinical trials was 5 days).

For Complicated Urinary Tract Infection (cUTI) including Pyelonephritis, the total duration of treatment could be increased to 14 days for patients with bacteraemia.

The duration of treatment should be guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress.

Special populations

Elderly patients

No dosage adjustment is considered necessary in elderly patients (≥ 65 years). The dose regimen should be adjusted if renal impairment is present (see section 5.2).

Patients with renal impairment

The following dose adjustment is recommended in patients with renal impairment (see sections 4.4 and 5.2).

Dose adjustments for Zavicefta for patients with an estimated creatinine clearance (CrCl) ≤50 ml/min are outlined in Table 2 below. The only information on dosing of Zavicefta for patients requiring dialysis is in the setting of intermittent haemodialysis. For other types of dialysis, it is suggested that the dose/frequency of ceftazidime-avibactam should follow local label/local guidelines for dosing of ceftazidime. For example, for a dose of 500 mg ceftazidime the dose of ceftazidime-avibactam would be 500 mg ceftazidime/125 mg avibactam.

Table 2 Recommended Dose for Patients with Renal Impairment*

Estimated CrCl (ml/min)[a]	Recommended Dosage Regimen Ceftazidime/Avibactam	Infusion Time (hours)	Frequency of Dosing (hourly)
50-31	1000 mg/250 mg	2	Every 8 hours
30-16	750 mg/187.5 mg	2	Every 12 hours
15 to 6	750 mg/187.5 mg[b]	2	Every 24 hours
<6	750 mg/187.5 mg[b]	2	Every 48 hours

[a] Creatinine Clearance (CrCl) calculated using the Cockcroft-Gault formula.
[b]Both ceftazidime and avibactam are haemodialyzable; thus, Zavicefta should be administered after haemodialysis on haemodialysis day.
* Dose recommendations are based on PK modelling.

In patients with impaired renal function, regular monitoring of estimated creatinine clearance is advised as in some patients, especially early in the course of their infection, the creatinine clearance estimated from serum creatinine can change quickly.

Haemodialysis

Both ceftazidime and avibactam are haemodialyzable; thus, Zavicefta should be administered after haemodialysis on haemodialysis day.

Haemofiltration

There is insufficient data to make specific dosage adjustment recommendations for patients undergoing continuous veno-venous haemofiltration.

Peritoneal dialysis

There is insufficient data to make specific dosage adjustment recommendations for patients undergoing peritoneal dialysis.

Patients with hepatic impairment

No dosage adjustment is considered necessary in patients with hepatic impairment (see section 5.2).Close clinical monitoring for safety and efficacy is advised.

Paediatric patients

Safety and efficacy in paediatric patients (< 18 years of age) have not been established (see section 5.2).

Method of administration

Zavicefta is administered by intravenous infusion over 120 minutes in an infusion volume of 100 ml (see section 6.6).

Constitution and compatibility

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

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
Hypersensitivity to the cephalosporin class of antibacterials.
Immediate and severe hypersensitivity (e.g. anaphylactic reaction) to any other type of β-lactam antibacterial agent (e.g. penicillins, monobactams or carbapenems).

4.4 Special warnings and special precautions for use

Hypersensitivity reactions

As with all β-lactam antibacterial agents, serious and occasionally fatal hypersensitivity reactions have been reported. In case of severe hypersensitivity reactions, treatment with Zavicefta must be discontinued immediately and adequate emergency measures must be initiated.

Before beginning treatment, it should be established whether the patient has a history of severe hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of β-lactam agent. Caution should be used if ceftazidime-avibactam is given to patients with a history of non-severe hypersensitivity to other β-lactam agents.

Limitation of the clinical data

Use of ceftazidime-avibactam to treat patients with Gram negative aerobic infections (see section 5.1 for species against which evidence of clinical efficacy has been observed) where therapeutic options are limited should be only after consultation with a physician with appropriate experience in the management of infectious diseases. Use of ceftazidime-avibactam in these infections is based on PK/PD extrapolations: no clinical studies have been conducted.

***Clostridium difficile*-associated diarrhoea**

Antibacterial agent-associated colitis and pseudo-membranous colitis have been reported with nearly all anti-bacterial agents, including ceftazidime-avibactam, 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 Zavicefta (see section 4.8). Discontinuation of therapy with Zavicefta and the administration of specific treatment for *Clostridium difficile* should be considered. Medicinal products that inhibit peristalsis should not be given.

Patients with renal impairment

Ceftazidime and avibactam are eliminated via the kidneys, therefore the dose should be reduced according to the degree of renal impairment. Patients with renal impairment should be closely monitored for both safety and efficacy. Neurological sequelae, including tremor, myoclonus, nonconvulsive status epilepticus, convulsion, encephalopathy and coma, have occasionally been reported with ceftazidime when the dose has not been reduced in patients with renal impairment (see section 4.2).

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function.

Non-susceptible organisms

Prolonged use may result in the overgrowth of non-susceptible organisms (e.g. enterococci, fungi), which may require interruption of treatment or other appropriate measures.

Non-druginterference

Ceftazidime does not interfere with enzyme-based tests for glycosuria, but slight interference (false-positive) may occur with copper reduction methods (Benedict's, Fehling's, Clinitest).

Ceftazidime does not interfere in the alkaline picrate assay for creatinine.

Direct antiglobulin test (DAGT or Coombs test) seroconversion and potential risk of haemolytic anaemia

Cephalosporin use may cause development of a positive direct antiglobulin test (DAGT**,** or Coombs test),which may interfere with the cross-matching of blood and/or may cause drug induced immune hemolyticanemia. While DAGT seroconversion in patients receiving Zavicefta was frequent in clinical studies, there was no evidence of haemolysis in patients who developed a positive DAGT on treatment

(see section 4.8). However, the possibility that haemolytic anaemia could occur in association with Zavicefta treatment cannot be ruled out. Patients experiencing anaemia during or after treatment with Zavicefta should be investigated for this possibility.

Controlled sodium diet

For patients who are on a controlled sodium diet, the following important information about the ingredients of ceftazidime and avibactam should be considered:

- 2 g powder for solution for infusion

Ceftazidime 2 g contains 4.52 mmol of sodium per vial; and

- 500 mg powder for solution for infusion

Avibactam 500 mg contains 1.92 mmol of sodium per vial.

4.5 Interaction with other medicinal products and other forms of interaction

Concurrent treatment with high doses of cephalosporins and nephrotoxic medicinal products such as aminoglycosides or potent diuretics (e.g. furosemide) may adversely affect renal function (see section 4.4).

Chloramphenicol is antagonistic *in vitro* with ceftazidime and other cephalosporins. The clinical relevance of this finding is unknown, but if concurrent administration of ceftazidime-avibactam with chloramphenicol is proposed, the possibility of antagonism should be considered.

Avibactam showed no significant inhibition of cytochrome P450 enzymes. Avibactam and ceftazidime showed no *in vitro* cytochrome P450 induction in the clinically relevant exposure range. Avibactam and ceftazidime do not inhibit the major renal or hepatic transporters in the clinically relevant exposure range, therefore the drug-drug interaction potential via these mechanisms is considered low.

In vitro, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake from the blood compartment and, thereby its excretion. Probenecid (a potent OAT inhibitor) inhibits this uptake by 56% to 70% *in vitro* and, therefore, has the potential to alter the elimination of avibactam when co-dosed. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-dosing of avibactam with probenecid is not recommended.

4.6 Pregnancy, lactation and fertility

Pregnancy

There is limited clinical data from the use of ceftazidime-avibactam in pregnant women. Animal embryofetal development studies conducted with ceftazidime or avibactam do not indicate harmful effects at exposures equivalent to therapeutic concentrations. Following administration of avibactam throughout pregnancy and lactation in the rat at maternal exposures greater than or equal to approximately 1.5times human therapeutic exposures, there were minor changes in the morphology of the kidney and ureters in the rat pups (see section 5.3).

Ceftazidime-avibactam should not be used during pregnancy unless clearly necessary and only if the potential benefit outweighs the possible risk.

Lactation

There are no data on human milk excretion of ceftazidime-avibactam. Ceftazidime is excreted in human milk in small quantities. It is unknown whether avibactam is excreted in human milk. Women who are breast-feeding should be treated with ceftazidime-avibactam only if clearly indicated. Interruption of breast-feeding is recommended.

Fertility

The effects of ceftazidime-avibactam on fertility in humans have not been studied. Animal studies with ceftazidime or avibactam do not indicate harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines (see section 4.8).

4.8 Undesirable effects

In seven Phase 2 and Phase 3 clinical trials,2024 adult patients were treated with Zavicefta. The most common adverse reactions occurring in ≥5% of patients treated with Zavicefta were Coombs direct test positive, nausea, and diarrhoea. These were usually mild or moderate in intensity.No clinically significant differences were observed in the safety profile across indications.

The following adverse reactions have been reported with ceftazidime alone and/or identified during all Phase 2 and Phase 3 clinical trials with Zavicefta (N=2024). Adverse reactions are classified according to frequency and System Organ Class. Frequency categories are derived from adverse reactions and/or potentially clinically significant laboratory abnormalities, and are defined according to the following conventions:

Very common (≥1/10)
Common (≥1/100 and <1/10)
Uncommon (≥1/1,000 and <1/100)
Rare (≥1/10,000 and <1/1000)
Very rare (<1/10,000)
Unknown (cannot be estimated from the available data)

If an event was not seen in the overall Phase 2 and Phase 3 pool but was a known ADR for ceftazidime alone, the frequency category for ceftazidime alone was used (including the category Unknown).

Table 3 Frequency of adverse reactions by system organ class

System Organ Class	Frequency	Adverse Reactions
Infections and infestations	Common	Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)
	Uncommon	Clostridium difficile colitis, Pseudomembranous colitis

Blood and lymphatic system disorders	Very common	Coombs direct test positive[1]
	Common	Eosinophilia, Thrombocytosis, Thrombocytopenia
	Uncommon	Neutropenia, Leukopenia, Lymphocytosis
	Unknown	Agranulocytosis, Haemolytic anemia
Immune system disorders	Unknown	Anaphylactic reaction
Nervous system disorders	Common	Headache, Dizziness
	Uncommon	Paraesthesia
Gastrointestinal disorders	Common	Diarrhoea , Abdominal pain, Nausea, Vomiting
	Uncommon	Dysgeusia
Hepatobiliary disorders	Common	Alanine aminotransferase increased, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Blood lactate dehydrogenase increased
	Unknown	Jaundice
Skin and subcutaneous tissue disorders	Common	Rash maculo-papular, Urticaria, Pruritus
	Unknown	Toxic epidermal necrolysis, Stevens-Johnson syndrome, Erythema multiforme, Angioedema, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)
Renal and urinary disorders	Uncommon	Blood creatinine increased, Blood urea increased, Acute kidney injury
	Very rare	Tubulointerstitial nephritis
General disorders and administration site conditions	Common	Infusion site thrombosis, Infusion site phlebitis, Pyrexia

[1]See section 4.4.

4.9 Overdose

Overdosage of ceftazidime-avibactam is unlikely, although overdosing could potentially occur in patients with moderate to severe renal impairment, and in end stage renal disease including patients undergoing haemodialysis (see section 4.4 and 5.2). Overdosing with ceftazidime-avibactam can lead to neurological sequelae including encephalopathy, convulsions and coma, due to the ceftazidime component.

Treatment for overdose should follow local standard medical practice. Both ceftazidime and avibactam can be partially removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following attachment to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. This broad spectrum cephalosporin is active against many important Gram-negative and Gram-positive bacterial pathogens *in vitro*. Avibactam is a non β-lactam, β-lactamase inhibitor that acts by forming a covalent adduct with the enzyme that is stable to hydrolysis. It inhibits both Ambler class A and class C β-lactamases, including extended-spectrum β-lactamases (ESBLs), KPC carbapenemases, and AmpC enzymes. Avibactam also inhibits the class D carbapenemase OXA-48, which does not significantly hydrolyze ceftazidime. Avibactam has no clinically relevant *in vitro* antibacterial activity. Avibactam did not induce transcription of bla_{AmpC} in *Enterobacter cloacae*, *Citrobacter freundii* or *Pseudomonas aeruginosain vitro* at concentrations used to treat patients.

Mechanism of resistance

Ceftazidime-avibactam is not active against metallo-β-lactamase-producing bacteria. Bacterial resistance mechanisms that could potentially affect ceftazidime-avibactam include mutant or acquired PBPs, decreased outer membrane permeability to either compound, active efflux of either compound, mutated or acquired β-lactamase enzymes insensitive to avibactam and able to hydrolyze ceftazidime.

Cross-resistance

An absence of cross-resistance between ceftazidime-avibactam and fluoroquinolones or aminoglycosides has been demonstrated *in vitro* using molecularly-characterized clinical isolates. Some isolates resistant to ceftazidime (and other cephalosporins) or to carbapenems are susceptible to ceftazidime-avibactam. There is cross-resistance withβ-lactam antibacterial agents, including carbapenems, when the mechanism is production of metallo-β-lactamases, such as VIM-2.

Interaction with other antimicrobial agents

In vitro interaction tests with ceftazidime-avibactam show ceftazidime-avibactam has little potential to antagonize or be antagonized by other antibiotics of various classes (e.g. metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin, tigecycline).

Susceptibility testing

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information on resistance is desirable, particularly when treating severe infections.

The susceptibility to ceftazidime-avibactam of a given clinical isolate should be determined by standard methods. Interpretations of test results should be made in accordance with local infectious diseases and clinical microbiology guidelines.

Pharmacokinetic/pharmacodynamic relationship

The antimicrobial activity of ceftazidime-avibactam against specific pathogens has been shown to best correlate with the percent time of free-drug concentration above the ceftazidime-avibactam minimum inhibitory concentration over the dose interval (%*f*T > MIC of ceftazidime-avibactam) for ceftazidime,

and the percent time of the free drug concentration above a threshold concentration over the dose interval (% *f*T>C_T) for avibactam.

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the pathogens, listed under each indication, that were susceptible to ceftazidime-avibactam *in vitro*.

Complicated intra-abdominal infections

Gram-negative micro-organisms

- *Citrobacter freundii*
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*

Complicated urinary-tract infections

Gram-negative micro-organisms

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Enterobacter cloacae*
- *Pseudomonas aeruginosa*

Hospital-acquired pneumonia including ventilator-associated pneumonia

Gram-negative micro-organisms

- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Serratia marcescens*
- *Pseudomonas aeruginosa*

Clinical efficacy has not been established against the following pathogens that are relevant to the approved indications although *in vitro* studies suggest that they would be susceptible to ceftazidime-avibactam in the absence of acquired mechanisms of resistance.

Gram-negative micro-organisms

- *Citrobacter koseri*
- *Enterobacter aerogenes*
- *Morganella morganii*
- *Proteus vulgaris*
- *Providencia rettgeri*

Ceftazidime-avibactam is active *in vitro* against *Streptococcus pyogenes* and *Streptococcus agalactiae*,but not generally active againstother clinically-important Gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA).

Clinical efficacy and safety

Complicated intra-abdominal infections

A total of 1058adults with complicated intra-abdominal infections (defined as infections that require surgical intervention and extend beyond the hollow viscus into the intraperitoneal space) were randomized and received treatment in two identical randomised, multi-centre, multinational, double-blind studies (RECLAIM 1 and RECLAIM 2) comparing Ceftazidime-avibactam (2000 mg of ceftazidime and 500 mg of avibactam) administered intravenously over 120 minutes every 8 hours plus metronidazole (500 mg) to meropenem (1000 mg) administered intravenously over 30 minutes. Treatment duration was 5 to 14 days. The modified intent-to-treat (MITT) population included all patients who met the disease definition of cIAI and received at least 1 dose of the study drug The clinically evaluable (CE) population included patients who had an appropriate diagnosis of cIAI and excluded patients with a bacterial species typically not expected to respond to both study drugs (i.e. *Acinetobacter baumannii* or *Stenotrophomonas*spp) and/or who had an important protocol deviation impacting the assessment of efficacy.

The primary efficacy endpoint was the clinical response at the Test of Cure (TOC) visit in the co-primary populations of the CE and MITT patients in Table 4 below.

Table 4 Clinical cure rate at TOC (RECLAIM MITT and CE analysis sets)

Analysis set	**Number (%) of patients**		
Response	**CAZ-AVI + MTZ**	**Meropenem**	**Difference(%) 95% CI**
MITT	(N=520)	(N=523)	
Clinical cure	429 (82.5)	444 (84.9)	-2.4 (-6.90, 2.10)
CE	(N=410)	(N=416)	
Clinical cure	376 (91.7)	385 (92.5)	-0.8 (-4.61, 2.89)

Clinical cure rates at TOC by pathogen in the microbiologically Modified Intent to Treat (mMITT) population for Gram-negative aerobes are shown in Table 5 below.

Table 5 Clinical cure rate at TOC by common (combined frequency of ≥10) Gram-negative baseline pathogen (RECLAIM mMITT analysis set)

	Number of patients					
	CAZ-AVI + MTZ (N=413)			**Meropenem (N=410)**		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**n**
Enterobacteriaceae	81.4	272	334	86.4	305	353

Table 5 **Clinical cure rate at TOC by common (combined frequency of ≥10) Gram-negative baseline pathogen (RECLAIM mMITT analysis set)**

	Number of patients					
	CAZ-AVI + MTZ (N=413)			Meropenem (N=410)		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**n**
*Citrobacter freundii*complex	77.8	14	18	75.0	9	12
Enterobacter aerogenes	80.0	4	5	100	5	5
Enterobacter cloacae	84.6	11	13	84.2	16	19
Escherichia coli	80.4	218	271	87.0	248	285
Klebsiella oxytoca	77.8	14	18	80.0	12	15
Klebsiella pneumoniae	78.4	40	51	75.5	37	49
Proteus mirabilis	62.5	5	8	77.8	7	9
Pseudomonas aeruginosa	85.7	30	35	94.4	34	36

A further 432 adults with complicated intra-abdominal infections were randomised and received treatment in a multi-centre, double-blind study (RECLAIM 3) conducted in 3 Asian countries (China, Republic of Korea and Vietnam). The patient population and key aspects of the study design were identical to RECLAIM apart from the primary efficacy endpoint of clinical response at the TOC visit being solely in the CE population (see Table 6 below).

Table 6 **Clinical cure rates at TOC (RECLAIM3 CE at TOC analysis set)**

	Number (%) of patients		
	CAZ-AVI + MTZ	**Meropenem**	**Difference(%) 95% CI**
	(N=177)	(N=184)	
Clinical cure	166 (93.8)	173 (94.0)	-0.2 (-5.53, 4.97)

Clinical cure rates at TOC by pathogen in the microbiologically modified Intent to Treat (mMITT) population for Gram-negative aerobes are shown in Table 7 below.

Table 7 **Clinical cure rates at TOCby common (combined frequency of ≥7) Gram-negative baseline pathogen (RECLAIM3 mMITT analysis set)**

	Number of patients					
	CAZ-AVI + MTZ (N=143)			Meropenem (N=152)		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**n**
Enterobacteriaceae	80.9	93	115	92.7	115	124
*Citrobacter freundii*complex	62.5	5	8		0	0

Table 7 **Clinical cure rates at TOCby common (combined frequency of ≥7) Gram-negative baseline pathogen (RECLAIM3 mMITT analysis set)**

	Number of patients					
	CAZ-AVI + MTZ (N=143)			Meropenem (N=152)		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**n**
Enterobacter cloacae	100	5	5	66.7	2	3
Escherichia coli	83.3	70	84	94.4	84	89
Klebsiella oxytoca	100	5	5	100	5	5
Klebsiella pneumoniae	82.1	23	28	88.6	31	35
Proteus mirabilis	66.7	2	3	100	5	5
Pseudomonas aeruginosa	82.4	14	17	85.0	17	20

Complicated urinary tract infections

A total of 1020 adults with documented complicated urinary tract infection (cUTI) (737 with acute pyelonephritis and 283 with cUTI without acute pyelonephritis) were randomised and received treatment in a phase III multicentre, double-blind, comparative study.Treatment was with either Ceftazidime-avibactam (2000 mg/500 mg) IV over 120 mins every 8 hours or doripenem 500 mg IV over 60 mins every 8 hours. There was an optional switch to oral therapy for patients who had clinical improvement as defined in the study protocol after a minimum of 5 days IV treatment. Total duration of antibiotic therapy (IV plus oral) was 10 days (optionally up to 14 if bacteraemic). The mMITT population included all patients with a confirmed cUTI diagnosis, received at least 1 dose of study treatment and had a study-qualifying pre-treatment urine culture containing 105 CFU/mL of a Gram-negative pathogen and no more than 2 species of microorganisms. Any patient with a Gram-positive pathogen, or a bacterial species not expected to respond to both study drugs was excluded.

The primary efficacy endpoint was per-patient microbiological response at the TOC visit in the mMITT analysis set.

Table 8 **Favourable per-patient microbiological response rate at TOC(RECAPTURE mMITT analysis set)**

		CAZ-AVI (N=393)	**Doripenem (N=417)**	**Difference (%) (95% CI)**
Per patient microbiological response	Favourable	304 (77.4)	296 (71.0)	6.4 (0.33, 12.36)

Favourable microbiological response rates at TOC by pathogen in the mMITT population are shown in Table 9 below.

Table 9 Favourable per-pathogen microbiological response rate at TOC by common (combined frequency of ≥10) baseline pathogen (RECAPTURE mMITT)

	Number of patients					
	CAZ-AVI (N=393)			Doripenem (N=417)		
Pathogen	**Favourable response rate (%)**	**Number of favourable responses**	**N**	**Favourable response rate (%)**	**Number of favourable responses**	**n**
Enterobacteriaceae	78.3	299	382	70.6	281	398
Enterobacter cloacae	54.5	6	11	69.2	9	13
Escherichia coli	78.4	229	292	71.9	220	306
Klebsiella pneumoniae	75.0	33	44	62.5	35	56
Proteus mirabilis	94.1	16	17	69.2	9	13
Pseudomonas aeruginosa	66.7	12	18	75.0	15	20

Hospital-acquired pneumonia

A total of 808 adults with nosocomial pneumonia (35% with VAP) were randomised and received treatment in a phase III double-blind, comparative study of Ceftazidime-avibactam (2000 mg/500 mg) IV over 120 mins every 8 hours or meropenem 1g IV over 30 mins every 8 hours. Treatment duration was 7 to 14 days. The clinically modified intent to treat (cMITT) population included patients who met the minimum disease criteria, received at least 1 dose of study treatment and who had properly obtained baseline respiratory or blood cultures demonstrating Gram-negative pathogens excluding patients with monomicrobial Gram-negative infections with species not expected to respond to both study drugs (e.g. *Acinetobacter* species or *Stenotrophomonas* species). The cMITT also included patients in whom no etiologic pathogens were identified from respiratory or blood cultures at baseline. The CE at TOC analyses set was the clinically evaluable subset of the cMITT.

The primary efficacy endpoint was the clinical response at the TOC visit in the co-primary populations of the cMITT and CE at TOC. See Table 10 below.

Table 10 Clinical cure rates at TOC (REPROVE cMITT and CE at TOC analysis sets)

		Number (%) of patients		
Analysis set	**Response**	**CAZ-AVI**	**Meropenem**	**Difference (%) 95% CI**
cMITT		(N=356)	(N=370)	
	Clinical cure	245 (68.8)	270 (73.0)	-4.2 (-10.76, 2.46)
CE at TOC		(N=257)	(N=270)	
	Clinical cure	199 (77.4)	211 (78.1)	-0.7 (-7.86, 6.39)

All-cause mortality rates at Day 28 (cMITT) was 8.4% (30/356) and 7.3% (27/370) ceftazidime-avibactam and meropenem treated patients, respectively.

Clinical cure rate and favourable microbiological response rate at TOC by pathogen in mMITT for Gram-negative aerobes are shown in Tables 11 and 12.

Table 11 Clinical cure rate at TOC by common (combined frequency of ≥10) Gram-negative baseline pathogen (REPROVE mMITT)

	Number of patients					
	CAZ-AVI (N=171)			Meropenem (N=184)		
Pathogen	**Cure rate (%)**	**Number of clinical cures**	**N**	**Cure rate (%)**	**Number of clinical cures**	**n**
Enterobacteriaceae	73.6	89	121	75.4	104	138
Enterobacter aerogenes	62.5	5	8	50.0	4	8
Enterobacter cloacae	92.3	24	26	54.5	12	22
Escherichia coli	64.7	11	17	75.0	15	20
Klebsiella pneumoniae	72.9	43	59	77.5	55	71
Proteus mirabilis	85.7	12	14	75.0	9	12
Serratia marcescens	73.3	11	15	92.3	12	13
Pseudomonas aeruginosa	60.3	35	58	74.5	35	47
Haemophilus influenzae	81.3	13	16	80.0	20	25

Table 12 Per-pathogen microbiological response at TOC by common (combined frequency of ≥10) Gram-negative baseline pathogen (REPROVE mMITT)

	Number of patients					
	CAZ-AVI (N=171)			Meropenem (N=184)		
Pathogen	**Favourable response rate (%)**	**Number of favourable responses**	**N**	**Favourable response rate (%)**	**Number of favourable responses**	**n**
Enterobacteriaceae						
Enterobacter aerogenes	62.5	5	8	62.5	5	8
Enterobacter cloacae	80.8	21	26	59.1	13	22
Escherichia coli	76.5	13	17	80.0	16	20
Klebsiella pneumoniae	62.7	37	59	74.6	53	71
Proteus mirabilis	78.6	11	14	66.7	8	12
Serratia marcescens	66.7	10	15	61.5	8	13
Pseudomonas aeruginosa	37.9	22	58	38.3	18	47
Haemophilus influenzae	87.5	14	16	92.0	23	25

5.2 Pharmacokinetic properties

Distribution

The human protein binding of both ceftazidime and avibactam is low, approximately 10% and 8%, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were comparable, about 22 L and 18 L, respectively in healthy adults following multiple doses of 2000 mg/500 mg ceftazidime-avibactam infused over 2 hours every 8 hours. Pharmacokinetic parameters of ceftazidime and avibactam following single and multiple dose administration of Zavicefta were similar to those

determined when ceftazidime or avibactam were administered alone. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% that of plasma, and a similar concentration time profile between ELF and plasma.

Ceftazidime and avibactam plasma exposure were comparable across patients with different indications, cIAI, cUTI and NP.

Penetration of ceftazidime into the intact blood-brain barrier is poor, resulting in low levels of ceftazidime in the CSF in the absence of inflammation. However, concentrations of 4 to 20 mg/L or more are achieved in the CSF when the meninges are inflamed. Avibactam penetration of the blood brain barrier has not been studied clinically, however, in rabbits with inflamed meninges, CSF exposures of ceftazidime and avibactam were 43% and 38% of plasma AUC, respectively. For ceftazidime, concentrations in excess of the MIC of ceftazidime-avibactam for common pathogens can be achieved in tissues such as bone, heart, bile, sputum, aqueous humour, synovial, pleural and peritoneal fluids. Ceftazidime crosses the placenta readily, and is excreted in the breast milk. Avibactam penetrates into the subcutaneous tissue at the site of skin infections, with tissue concentrations approximately equal to free drug concentrations in plasma.

Biotransformation

Ceftazidime is not metabolized. No metabolism of avibactam was observed in human liver preparations (microsomes and hepatocytes). Unchanged avibactam was the major drug-related component in human plasma and urine following dosing with [^{14}C]-avibactam.

Elimination

The terminal half-life (t½) of both ceftazidime and avibactam is about 2 h after IV administration. Ceftazidime is excreted unchanged into the urine by glomerular filtration; approximately 80 - 90% of the dose is recovered in the urine within 24 h. Avibactam is excreted unchanged into the urine with a renal clearance of approximately 158 ml/min, suggesting active tubular secretion in addition to glomerular filtration; approximately 97% of the dose is recovered in the urine, 95% within 12 h. Less than 1% of ceftazidime is excreted via the bile and less than 0.25% of avibactam is excreted into faeces.

Linearity/non-linearity

The pharmacokinetics of both ceftazidime and avibactam are approximately linear across the dose range studied (50 mg to 2000 mg) for a single IV administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple IV infusions of 2000 mg/500 mg of ceftazidime-avibactam administered every 8 hours for up to 11 days in healthy adults with normal renal function.

Special populations

Patients with renal impairment

Elimination of ceftazidime and avibactam is decreased in patients with moderate or severe renal impairment, and end stage renal disease including patients undergoing haemodialysis; the dose should be reduced in patients with CrCl ≤50 ml/min) (see section 4.2).

Patients with hepatic impairment

Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g IV every 8 hours for 5 days, provided renal function was not impaired. The

pharmacokinetics of ceftazidime in patients with severe hepatic impairment has not been established. The pharmacokinetics of avibactam in patients with any degree of hepatic impairment has not been studied.

As ceftazidime and avibactam do not appear to undergo significant hepatic metabolism, the systemic clearance of either drug is not expected to be significantly altered by hepatic impairment. Therefore, no dosage adjustment of ceftazidime-avibactam is recommended for patients with hepatic impairment(see section 4.2)**.**

Elderly patients

The reduced clearance observed in elderly patients was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life ranged from 3.5 to 4 hours following single or 7 days repeated every 12 hours dosing of 2 g IV bolus injections in elderly patients 80 years or older.

Following single dose IV administration of 500 mg avibactam as a 30-minute IV infusion, the elderly had a slower terminal half-life of avibactam, which may be attributed to age related decrease in renal clearance. Dosage adjustment for ceftazidime-avibactam is not required in elderly subjects (≥ 65 years of age) with CrCl> 50 ml/min.

Paediatric patients

The safety and efficacy of Zavicefta in paediatric patients (< 18 years of age)have not been established.

Gender

The pharmacokinetics of ceftazidime-avibactam was similar between males and females. No dose adjustment is required based on sex.

Race

Based on a population pharmacokinetic analysis, no dose adjustment of ceftazidime-avibactam is required based on race.

5.3 Preclinical safety data

Genetic toxicology

For ceftazidime a mouse Micronucleus test and an Ames test were both negative for mutagenic effects. Carcinogenicity studies have not been conducted.In genotoxicity assays with avibactam, there was no induction of gene mutation in the *in vitro* bacterial reverse mutation tests, nor were there any indications of genotoxicity in an *in vitro* unscheduled DNA synthesis test in rat liver cells or an *in vitro* micronucleus test in mouse lymphoma cells. In cultured human lymphocytes, statistically significant increases in chromosomal aberrations were observed under a single treatment condition (44h harvest time, -S9). As these findings were not replicated in an independent study, the results are considered to be of limited biological relevance. When administered up to the limit dose of 2 g/kg IV, avibactam was negative in a rat *in vivo* micronucleus assay. Carcinogenicity studies have not been conducted. No genetic toxicology studies have been conducted on ceftazidime-avibactam.

Reproductive toxicology

Reproduction studies have been performed with ceftazidime in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus.In pregnant rabbits

at exposures of avibactam approximately 8 fold higher than those observed in humans at 0.5 g three times daily there was a significant effect on maternal food consumption and a slight effect on fetal weight and slight retardation of ossification of a few bones in the fetus. In the rat, no adverse effects were observed on embryofetal development or fertility. Following administration of avibactam throughout pregnancy and lactation in the rat, there was no effect on pup survival, growth or development, however there was an increase in incidence of dilation of the renal pelvis and ureters in less than 10% of the rat pups at maternal exposures greater than or equal to approximately 1.5 times human therapeutic exposures. No reproductive toxicology studies have been conducted on ceftazidime-avibactam.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium carbonate

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

Do not use Zavicefta after the expiry date which is stated on the Carton/Vial label after EXP:. The expiry date refers to the last day of that month.

After reconstitution:
The reconstituted vial should be used immediately.

After dilution:
Once the intravenous solution is prepared with diluents listed in section 6.6 it should be administered within 12 hours of preparation. The chemical and physical in-use stability has been demonstrated for up to 24 hours at 2-8°C. Once removed from refrigeration the diluted product must be stored at room temperature and used within 12 hours.

From a microbiological point of view, the medicinal 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 to 8ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store below 30°C.

Store in the original package in order to protect from light.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

20 ml glass vial (Type 1) closed with a rubber (halobutyl) stopper and aluminium seal with flip-off cap.

The medicinal product is supplied in packs of 10 vials.

6.6 Instructions for use, handling and disposal

The powder must be reconstituted with sterile water for injections and the resulting concentrate must then be immediately diluted prior to use. The reconstituted solution is a pale yellow solution that is free of any particles.

Standard aseptic techniques should be used for solution preparation and administration.

1. Introduce the syringe needle through the vial closure and inject 10 ml of sterile water for injection.

2. Withdraw the needle and shake the vial to give a clear solution.

3. Do not insert a gas relief needle until the product has dissolved. Insert a gas relief needle through the vial closure to relieve the internal pressure.

4. Transfer the entire contents (approximately 12.0 ml) of the resultant solution to an infusion bag immediately. Reduced doses may be achieved by transfer of an appropriate volume of the resultant solution to an infusion bag, based upon ceftazidime and avibactam content of 167.3 mg/ml and 41.8 mg/ml, respectively. A dose of 1000 mg/250 mg or 750 mg/187.5 mg is achieved with 6.0 ml or 4.5 ml aliquots, respectively.

Note: To preserve product sterility, it is important that the gas relief needle is not inserted through the vial closure before the product is dissolved.

Vials of ceftazidime-avibactam powder should be reconstituted with 10 ml of sterile water for injections, followed by shaking until the content dissolves. An infusion bag may contain any of the following: sodium chloride 9 mg/ml (0.9%) solution for injection, dextrose 50 mg/ml (5%) solution for injection, sodium chloride 4.5 mg/ml and dextrose 25 mg/ml solution for injection (0.45% sodium chloride and 2.5% dextrose) or Lactated Ringer's solution. A 100 ml infusion bag can be used to prepare the infusion, based on the patient's volume requirements. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes.

Each vial is for single use only.

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

7. MARKING AUTHORIZATION HOLDER AND MANUFACTURER

MANUFACTURED BY

ACS Dobfar S.p.A
Via Alessandro Fleming 2,
Verona 37135,
Italy

8. MARKING AUTHORIZATION NUMBER

06572/07274/VAR/2020

9. DATE OF MARKET AUTHORISATION

13-10-2021

10. DATE OF REVISION OF THE TEXT

February 2021