▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.

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

Excipient with known effect: each vial contains 6.44 mmol of sodium (approximately 148 mg).

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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

A white to yellow powder.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

- Complicated intra-abdominal infection (cIAI)
- Complicated urinary tract infection (cUTI), including pyelonephritis
- Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP)

Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (see sections 4.2, 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

It is recommended that Zavicefta should be used to treat infections due to aerobic Gram-negative organisms in adult patients with limited treatment options only after consultation with a physician with appropriate experience in the management of infectious diseases (see section 4.4).

Posology

Table 1 shows the recommended intravenous dose for patients with estimated creatinine clearance (CrCL) ≥ 51 mL/min (see sections 4.4 and 5.1).

Table 1 Recommended intravenous dose for patients with estimated CrCL ≥ 51 mL/min[1]

| Type of infection | Dose of ceftazidime/avibactam | Frequency | Infusion time | Duration of treatment |
|---|---|---|---|---|
| Complicated IAI[2, 3] | 2 g/0.5 g | Every 8 hours | 2 hours | 5-14 days |
| Complicated UTI, including pyelonephritis[3] | 2 g/0.5 g | Every 8 hours | 2 hours | 5-10 days[4] |
| Hospital-acquired pneumonia, including VAP[3] | 2 g/0.5 g | Every 8 hours | 2 hours | 7-14 days |
| Infections due to aerobic Gram-negative organisms in patients with limited treatment options[2,3] | 2 g/0.5 g | Every 8 hours | 2 hours | Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[5] |

[1] CrCL estimated using the Cockcroft-Gault formula

[2] To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process

[3] To be used in combination with an antibacterial agent active against Gram-positive pathogens when these are known or suspected to be contributing to the infectious process

[4] The total duration shown may include intravenous Zavicefta followed by appropriate oral therapy

[5] There is very limited experience with the use of Zavicefta for more than 14 days

Special populations

*Elderly*

No dosage adjustment is required in elderly patients (see section 5.2).

*Renal impairment*

No dosage adjustment is required in patients with mild renal impairment (estimated CrCL ≥ 51 - ≤ 80 mL/min) (see section 5.2).

Table 2 shows the recommended dose adjustments for patients with estimated CrCL ≤ 50 mL/min (see sections 4.4 and 5.2).

Table 2 Recommended intravenous doses for patients with estimated CrCL ≤ 50 mL/min[1]

| Estimated CrCL (mL/min) | Dose regimen[2] | Frequency | Infusion time |
|---|---|---|---|
| 31-50 | 1 g/0.25 g | Every 8 hours | 2 hours |
| 16-30 | 0.75 g/0.1875 g | Every 12 hours | 2 hours |
| 6-15 | 0.75 g/0.1875 g | Every 24 hours | 2 hours |
| ESRD including on haemodialysis[3] | 0.75 g/0.1875 g | Every 48 hours | 2 hours |

[1] CrCL estimated using the Cockcroft-Gault formula

[2] Dose recommendations are based on pharmacokinetic modelling

[3] Ceftazidime and avibactam are removed by haemodialysis (see sections 4.9 and 5.2). Dosing of Zavicefta on haemodialysis days should occur after completion of haemodialysis.

*Hepatic impairment*

No dosage adjustment is required in patients with hepatic impairment (see section 5.2).

*Paediatric population*
Safety and efficacy in children and adolescents below 18 years of age have not yet been established.

Currently available data are described in section 4.8 but no recommendation on a posology can be made.

Method of administration

Zavicefta is administered by intravenous infusion over 120 minutes in an infusion volume of 100 mL.

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 any cephalosporin antibacterial agent.

Severe hypersensitivity (e.g. anaphylactic reaction, severe skin reaction) to any other type of β-lactam antibacterial agent (e.g. penicillins, monobactams or carbapenems).

## 4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity reactions are possible (see sections 4.3 and 4.8). In case of 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 hypersensitivity reactions to ceftazidime, to other cephalosporins or to any other type of β-lactam antibacterial agent. Caution should be used if ceftazidime/avibactam is given to patients with a history of non-severe hypersensitivity to penicillins, monobactams or carbapenems.

*Clostridium difficile*-associated diarrhoea

*Clostridium difficile*-associated diarrhoea has been reported with ceftazidime/avibactam, and can range in severity from mild to life-threatening. This diagnosis should be considered 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.

Renal impairment

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

In patients with renal impairment, close monitoring of estimated creatinine clearance is advised. In some patients, the creatinine clearance estimated from serum creatinine can change quickly, especially early in the course of treatment for the infection.

Nephrotoxicity

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.

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

Ceftazidime/avibactam 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 haemolytic anaemia (see section 4.8). While DAGT seroconversion in patients receiving Zavicefta was very common in clinical studies (the estimated range of seroconversion across Phase 3 studies was 3.2% to 20.8% in patients with a negative Coombs test at baseline and at least one follow-up test), there was no evidence of haemolysis in patients who developed a positive DAGT on treatment. 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.

Limitations of the clinical data

Clinical efficacy and safety studies of Zavicefta have been conducted in cIAI, cUTI and HAP (including VAP).

*Complicated intra-abdominal infections*
In two studies in patients with cIAI, the most common diagnosis (approximately 42%) was appendiceal perforation or peri-appendiceal abscess. Approximately 87% of patients had APACHE II scores of ≤ 10 and 4.0% had bacteraemia at baseline. Death occurred in 2.1% (18/857) of patients who received Zavicefta and metronidazole and in 1.4% (12/863) of patients who received meropenem.

Among a subgroup with baseline CrCL 30 to 50 mL/min death occurred in 16.7% (9/54) of patients who received Zavicefta and metronidazole and 6.8% (4/59) of patients who received meropenem. Patients with CrCL 30 to 50 mL/min received a lower dose of Zavicefta than is currently recommended for patients in this sub-group.

*Complicated urinary tract infections*
In two studies in patients with cUTI, 381/1091 (34.9%) patients were enrolled with cUTI without pyelonephritis while 710 (65.1%) were enrolled with acute pyelonephritis (mMITT population). A total of 81 cUTI patients (7.4%) had bacteraemia at baseline.

*Hospital-acquired pneumonia, including ventilator-associated pneumonia*
In a single study in patients with nosocomial pneumonia 280/808 (34.7%) had VAP and 40/808 (5.0%) were bacteraemic at baseline.

*Patients with limited treatment options*
The use of ceftazidime/avibactam to treat patients with infections due to Gram-negative aerobic pathogens who have limited treatment options is based on experience with ceftazidime alone and on analyses of the pharmacokinetic-pharmacodynamic relationship for ceftazidime/avibactam (see section 5.1).

Spectrum of activity of ceftazidime/avibactam

Ceftazidime has little or no activity against the majority of Gram-positive organisms and anaerobes (see sections 4.2 and 5.1). Additional antibacterial agents should be used when these pathogens are known or suspected to be contributing to the infectious process.

The inhibitory spectrum of avibactam includes many of the enzymes that inactivate ceftazidime, including Ambler class A β-lactamases and class C β-lactamases. Avibactam does not inhibit class B enzymes (metallo-β-lactamases) and is not able to inhibit many of the class D enzymes (see section 5.1).

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.

Interference with laboratory tests

Ceftazidime may interfere with copper reduction methods (Benedict's, Fehling's, Clinitest) for detection of glycosuria leading to false positive results. Ceftazidime does not interfere with enzyme-based tests for glycosuria.

Controlled sodium diet

Each vial contains a total of 6.44 mmol of sodium (approximately 148 mg), equivalent to 7.4% of the WHO recommended maximum daily intake for sodium. The maximum daily dose of this product is equivalent to 22.2% of the WHO recommended maximum daily intake for sodium.

This should be considered when administering Zavicefta to patients who are on a controlled sodium diet.

## 4.5 Interaction with other medicinal products and other forms of interaction

*In vitro*, avibactam is a substrate of OAT1 and OAT3 transporters which might contribute to the active uptake of avibactam from the blood compartment and therefore affect 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. Since a clinical interaction study of avibactam and probenecid has not been conducted, co-administration of avibactam with probenecid is not recommended.

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

Clinical data have demonstrated that there is no interaction between ceftazidime and avibactam, and between ceftazidime/avibactam and metronidazole.

*Other types 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 due to the possibility of antagonism *in vivo* this drug combination should be avoided.

## 4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies with ceftazidime do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Animal studies with avibactam have shown reproductive toxicity without evidence of teratogenic effects (see section 5.3).

Ceftazidime/avibactam should only be used during pregnancy if the potential benefit outweighs the possible risk.

Breast-feeding

Ceftazidime is excreted in human milk in small quantities. It is unknown whether avibactam is excreted in human milk. A risk to newborns/infants cannot be excluded. A decision must be made whether to discontinue breast feeding or to discontinue/abstain from ceftazidime/avibactam therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility

The effects of ceftazidime/avibactam on fertility in humans have not been studied. No data are available on animal studies with ceftazidime. Animal studies with avibactam do not indicate harmful effects with respect to fertility (see section 5.3).

## 4.7 Effects on ability to drive and use machines

Undesirable effects may occur (e.g. dizziness), which may influence the ability to drive and use machines following administration of Zavicefta (see section 4.8).

## 4.8 Undesirable effects

Summary of the safety profile

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. Nausea and diarrhoea were usually mild or moderate in intensity.

Tabulated list of adverse reactions

The following adverse reactions have been reported with ceftazidime alone and/or identified during the Phase 2 and Phase 3 trials with Zavicefta. 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)

Table 3 Frequency of adverse reactions by system organ class

| **System Organ Class** | **Very common** | **Common** | **Uncommon** | **Very rare** | **Unknown** |
|---|---|---|---|---|---|
| Infections and infestations | | Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis) | Clostridium difficile colitis<br><br>Pseudomembranous colitis | | |
| Blood and lymphatic system disorders | Coombs direct test positive | Eosinophilia<br><br>Thrombocytosis<br><br>Thrombocytopenia | Neutropenia<br><br>Leukopenia<br><br>Lymphocytosis | | Agranulocytosis<br><br>Haemolytic anaemia |

| | | | | | |
|---|---|---|---|---|---|
| Immune system disorders | | | | | Anaphylactic reaction |
| Nervous system disorders | | Headache<br><br>Dizziness | Paraesthesia | | |
| Gastrointestinal disorders | | Diarrhoea<br><br>Abdominal pain<br><br>Nausea<br><br>Vomiting | Dysgeusia | | |
| Hepatobiliary disorders | | Alanine aminotransferase increased<br><br>Aspartate aminotransferase increased<br><br>Blood alkaline phosphatase increased<br><br>Gamma-glutamyltransferase increased<br><br>Blood lactate dehydrogenase Increased | | | Jaundice |
| Skin and subcutaneous tissue disorders | | Rash maculo-papular<br><br>Urticaria<br><br>Pruritus | | | Toxic epidermal necrolysis<br><br>Stevens-Johnson syndrome<br><br>Erythema multiforme<br><br>Angioedema<br><br>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) |

| | | | | | |
|---|---|---|---|---|---|
| Renal and urinary disorders | | | Blood creatinine increased<br><br>Blood urea increased<br><br>Acute kidney injury | Tubulointerstitial nephritis | |
| General disorders and administration site conditions | | Infusion site thrombosis<br><br>Infusion site phlebitis<br><br>Pyrexia | | | |

Paediatric population

The safety assessment in children is based on the safety data from 1 trial in which 61 paediatric patients aged from 3 years to less than 18 years with cIAI received Zavicefta. Overall, the safety profile in these 61 children was similar to that observed in the adult population with cIAI.

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.

United Kingdom
Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland
Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

### 4.9 Overdose

Overdose with ceftazidime/avibactam can lead to neurological sequelae including encephalopathy, convulsions and coma, due to the ceftazidime component.

Serum levels of ceftazidime can be reduced by haemodialysis or peritoneal dialysis. During a 4-hour haemodialysis period, 55% of the avibactam dose was removed.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, ceftazidime, combinations, ATC code: J01DD52

Mechanism of action

Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death. 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 and some class D enzymes, including extended-spectrum β-lactamases (ESBLs), KPC and OXA-48 carbapenemases, and AmpC enzymes. Avibactam does not inhibit class B enzymes (metallo-β-lactamases) and is not able to inhibit many class D enzymes.

Resistance

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, and β-lactamase enzymes refractory to inhibition by avibactam and able to hydrolyse ceftazidime.

Antibacterial activity in combination with other antibacterial agents

No synergy or antagonism was demonstrated in *in vitro* drug combination studies with ceftazidime/avibactam and metronidazole, tobramycin, levofloxacin, vancomycin, linezolid, colistin and tigecycline.

Susceptibility testing breakpoints

Minimum Inhibitory Concentration (MIC) breakpoints established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for ceftazidime/avibactam are as follows:

| **Organisms** | **Susceptible** | **Resistant** |
|---|---|---|
| *Enterobacteriaceae* | ≤8 mg/L | >8 mg/L |
| *Pseudomonas aeruginosa* | ≤8 mg/L | >8 mg/L |

Pharmacokinetic/pharmacodynamic relationship

The antimicrobial activity of ceftazidime 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 avibactam the PK-PD index is the percent time of the free drug concentration above a threshold concentration over the dose interval (% *f*T >$C_T$).

Clinical efficacy against specific pathogens

Efficacy has been demonstrated in clinical studies against the following pathogens 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*

*In-vitro* data indicate that the following species are not susceptible to ceftazidime/avibactam.

- *Staphylococcus aureus* (methicillin-susceptible and methicillin-reistant)
- Anaerobes
- *Enterococcus* spp.
- *Stenotrophomonas maltophilia*
- *Acinetobacter* spp.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Zavicefta in one or more subsets of the paediatric population in the treatment of intra-abdominal infections, urinary tract infections, pneumonia and Gram-negative bacterial infections (see section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

Distribution

The human protein binding of both ceftazidime and avibactam is approximately 10% and 8%, respectively. The steady-state volumes of distribution of ceftazidime and avibactam were 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. Both ceftazidime and avibactam penetrate into human bronchial epithelial lining fluid (ELF) to the same extent with concentrations around 30% of those in plasma. The concentration time profiles are similar for ELF and plasma.

Penetration of ceftazidime into the intact blood-brain barrier is poor. Ceftazidime 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. Ceftazidime crosses the placenta readily, and is excreted in the breast milk.

Biotransformation

Ceftazidime is not metabolised. 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 ($t_{½}$) of both ceftazidime and avibactam is about 2 h after intravenous 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 avibactam 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 intravenous administration. No appreciable accumulation of ceftazidime or avibactam was observed following multiple intravenous 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

*Renal impairment*
Elimination of ceftazidime and avibactam is decreased in patients with moderate or severe renal impairment. The average increases in avibactam AUC are 3.8-fold and 7-fold in subjects with moderate and severe renal impairment, see section 4.2.

*Hepatic impairment*
Mild to moderate hepatic impairment had no effect on the pharmacokinetics of ceftazidime in individuals administered 2 g intravenously 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 active substance is not expected to be significantly altered by hepatic impairment.

*Elderly patients (≥65 years)*
Reduced clearance of ceftazidime was observed in elderly patients, which was primarily due to age-related decrease in renal clearance of ceftazidime. The mean elimination half-life of ceftazidime ranged from 3.5 to 4 hours following intravenous bolus dosing with 2 g every 12 hours in elderly patients aged 80 years or older.

Following a single intravenous 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.

*Gender and race*
The pharmacokinetics of ceftazidime/avibactam is not significantly affected by gender or race.

### 5.3 Preclinical safety data

Ceftazidime

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproduction toxicity or genotoxicity. Carcinogenicity studies have not been conducted with ceftazidime.

Avibactam

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity or genotoxicity. Carcinogenicity studies have not been conducted with avibactam.

Reproduction toxicity

In pregnant rabbits administered avibactam at 300 and 1000 mg/kg/day, there was a dose-related lower mean foetal weight and delayed ossification, potentially related to maternal toxicity. Plasma exposure levels at maternal and foetal NOAEL (100 mg/kg/day) indicate moderate to low margins of safety.
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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium carbonate (anhydrous)

### 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

Dry powder

3 years.

After reconstitution

The reconstituted vial should be used immediately.

After dilution

The chemical and physical in-use stability has been demonstrated for up to 24 hours at 2 - 8°C, followed by up to 12 hours at not more than 25ºC.

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 - 8ºC, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

### 6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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 Special precautions for disposal and other handling

The powder must be reconstituted with water for injections and the resulting concentrate must then be immediately diluted prior to use. The reconstituted solution is pale yellow solution and free of 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 injections.
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. MARKETING AUTHORISATION HOLDER

Pfizer Ireland Pharmaceuticals

Operations Support Group
Ringaskiddy, County Cork
Ireland

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1109/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 June 2016

## 10. DATE OF REVISION OF THE TEXT

04/2019

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

Ref: ZV 5_0