ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
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

<table>
<thead>
<tr>
<th>Type of infection</th>
<th>Dose of ceftazidime/avibactam</th>
<th>Frequency</th>
<th>Infusion time</th>
<th>Duration of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complicated IAI&lt;sup&gt;1, 3&lt;/sup&gt;</td>
<td>2 g/0.5 g Every 8 hours 2 hours</td>
<td>5-14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated UTI, including pyelonephritis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2 g/0.5 g Every 8 hours 2 hours</td>
<td>5-10 days&lt;sup&gt;4&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital-acquired pneumonia, including VAP&lt;sup&gt;3&lt;/sup&gt;</td>
<td>2 g/0.5 g Every 8 hours 2 hours</td>
<td>7-14 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections due to aerobic Gram-negative organisms in patients with limited treatment options&lt;sup&gt;2, 3&lt;/sup&gt;</td>
<td>2 g/0.5 g Every 8 hours 2 hours</td>
<td>Guided by the severity of the infection, the pathogen(s) and the patient’s clinical and bacteriological progress&lt;sup&gt;5&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> CrCL estimated using the Cockcroft-Gault formula
<sup>2</sup> To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process
<sup>3</sup> 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
<sup>4</sup> The total duration shown may include intravenous Zavicefta followed by appropriate oral therapy
<sup>5</sup> 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<sup>1</sup>

<table>
<thead>
<tr>
<th>Estimated CrCL (mL/min)</th>
<th>Dose regimen&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Frequency</th>
<th>Infusion time</th>
</tr>
</thead>
<tbody>
<tr>
<td>31-50</td>
<td>1 g/0.25 g</td>
<td>Every 8 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>16-30</td>
<td>0.75 g/0.1875 g</td>
<td>Every 12 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>6-15</td>
<td>0.75 g/0.1875 g</td>
<td>Every 24 hours</td>
<td>2 hours</td>
</tr>
<tr>
<td>ESRD including on haemodialysis&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.75 g/0.1875 g</td>
<td>Every 48 hours</td>
<td>2 hours</td>
</tr>
</tbody>
</table>

<sup>1</sup> CrCL estimated using the Cockcroft-Gault formula
<sup>2</sup> Dose recommendations are based on pharmacokinetic modelling
<sup>3</sup> 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. No data are available.
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). 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**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
<th>Uncommon</th>
<th>Very rare</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td></td>
<td>Candidiasis (including Vulvovaginal candidiasis and Oral candidiasis)</td>
<td>Clostridium difficile colitis</td>
<td>Pseudomembranous colitis</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Coombs direct test positive</td>
<td>Eosinophilia</td>
<td>Neutropenia</td>
<td></td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thrombocytosis</td>
<td>Leukopenia</td>
<td>Lymphocytosis</td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td>Immune system</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anaphylactic</td>
</tr>
</tbody>
</table>

7
<table>
<thead>
<tr>
<th>disorders</th>
<th>reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>Paraesthesia</td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>Dysgeusia</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase</td>
<td>Jaundice</td>
</tr>
<tr>
<td>increased</td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td></td>
</tr>
<tr>
<td>increased</td>
<td></td>
</tr>
<tr>
<td>Blood alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td>increased</td>
<td></td>
</tr>
<tr>
<td>Gamma-glutamyltransferase</td>
<td></td>
</tr>
<tr>
<td>increased</td>
<td></td>
</tr>
<tr>
<td>Blood lactate dehydrogenase</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Erythema multiforme</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
</tr>
<tr>
<td></td>
<td>Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)</td>
</tr>
</tbody>
</table>
### Renal and urinary disorders

- Blood creatinine increased
- Blood urea increased
- Acute kidney injury

### General disorders and administration site conditions

- Infusion site thrombosis
- Infusion site phlebitis
- Pyrexia

### Tubulointerstitial nephritis

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**Reporting of suspected adverse reactions**

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

**4.9 Overdose**

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:

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>≤8 mg/L</td>
<td>&gt;8 mg/L</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>≤8 mg/L</td>
<td>&gt;8 mg/L</td>
</tr>
</tbody>
</table>

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 (%fT >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 (%fT >Cₜ).

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-resistant)
- 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 ($t_{1/2}$) 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 25°C.

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 - 8°C, 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 Services 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

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT
A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

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

GlaxoSmithKline Manufacturing S.p.A
VIA A. FLEMING, 2
VERONA 37135
ITALY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- Periodic safety update reports

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

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- Risk Management Plan (RMP)

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

An updated RMP should be submitted:

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

LABELLING AND PACKAGE LEAFLET
A. LABELLING
PARTICULARS TO APPEAR ON THE OUTER PACKAGING CARTON

1. NAME OF THE MEDICINAL PRODUCT
ZAVICEFTA 2 g/0.5g powder for concentrate for solution for infusion ceftazidime/avibactam

2. STATEMENT OF ACTIVE SUBSTANCE(S)
Each vial contains ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.

3. LIST OF EXCIPIENTS
Contains sodium carbonate – see package leaflet for further details.

4. PHARMACEUTICAL FORM AND CONTENTS
powder for concentrate for solution for infusion
10 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION
Read the package leaflet before use.
Intravenous use
Dilute before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN
Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE
EXP

9. SPECIAL STORAGE CONDITIONS
Store in the original package in order to protect from light.
10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Ireland Pharmaceuticals
Operations Services Group
Ringaskiddy, County Cork
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1109/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:
MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

ZAVICEFTA 2 g/0.5 g powder for concentrate
ceftazidime/avibactam
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

ceftazidime 2 g/avibactam 0.5 g

6. OTHER
B.PACKAGE LEAFLET
1. What Zavicefta is and what it is used for

What Zavicefta is
Zavicefta is an antibiotic medicine that contains two active substances ceftazidime and avibactam.
- Ceftazidime belongs to the group of antibiotics called “cephalosporins”. It can kill many types of bacteria.
- Avibactam is a “beta-lactamase inhibitor” that helps ceftazidime kill some bacteria that it cannot kill on its own.

What Zavicefta is used for
Zavicefta is used in adults to treat:
- infections of the stomach and gut (abdomen)
- infections of the bladder or kidneys called “urinary tract infections”
- an infection of the lungs called “pneumonia”
- infections caused by bacteria that other antibiotics may not be able to kill

How Zavicefta works
Zavicefta works by killing certain types of bacteria, which can cause serious infections.

2. What you need to know before you use Zavicefta

Do not use Zavicefta if:
- you are allergic to ceftazidime, avibactam or any of the other ingredients of this medicine (listed in section 6)
- you are allergic to other cephalosporin antibiotics
- you have ever had a severe allergic reaction to other antibiotics belonging to the penicillin or carbapenem groups
Do not use Zavicefta if any of the above apply to you. If you are not sure, talk to your doctor or nurse before using Zavicefta.

**Warnings and precautions**
Talk to your doctor or nurse before using Zavicefta if:
- you have ever had any allergic reaction (even if only a skin rash) to other antibiotics belonging to the penicillin or carbapenem groups
- you have kidney problems - your doctor may give you a lower dose to make sure you don’t get too much medicine. This could cause symptoms such as fits (see section If you use more Zavicefta than you should)

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before using Zavicefta.

Talk to your doctor or nurse if you suffer from diarrhoea during your treatment.

**Other infections**
There is a small possibility that you may get a different infection caused by another bacteria during or after treatment with Zavicefta. These include thrush (fungal infections of the mouth or genital area).

**Lab tests**
Tell your doctor that you are taking Zavicefta if you are going to have any tests. This is because you may get an abnormal result with a test called “DAGT” or “Coombs”. This test looks for antibodies that fight against your red blood cells.

Zavicefta can also affect the results of some urine tests for sugar. Tell the person taking the sample that you have been given Zavicefta.

**Children and adolescents**
Zavicefta should not be used in children and adolescents. This is because it is not known if the medicine is safe to use in these age groups.

**Other medicines and Zavicefta**
Tell your doctor or nurse if you are using, have recently used or might use any other medicines.

Talk to your doctor before using Zavicefta if you are taking any of the following medicines:
- an antibiotic called chloramphenicol
- a type of antibiotic called an aminoglycoside – such as gentamicin, tobramycin
- a water tablet called furosemide
- a medicine for gout called probenecid

Tell your doctor before using Zavicefta if any of the above apply to you.

**Pregnancy and breast-feeding**
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

**Driving and using machines**
Zavicefta may make you feel dizzy. This may affect you being able to drive, use tools or machines.

**Zavicefta contains sodium**
For patients on a sodium-controlled diet, each vial contains approximately 148 mg of sodium.

3. **How to use Zavicefta**

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

**How much to use**
The recommended dose is one vial (2 g of ceftazidime and 0.5 g of avibactam), every 8 hours.
It is given as a drip into a vein – this will take about 2 hours.

A course of treatment usually lasts from 5 to up to 14 days, depending on the type of infection you have and how you respond to treatment.

**People with kidney problems**
If you have kidney problems your doctor may lower your dose. This is because Zavicefta is removed from your body by the kidneys.

**If you use more Zavicefta than you should**
Zavicefta will be given to you by a doctor or a nurse, so it is unlikely you will be given the wrong dose. However, if you have side effects or think you have been given too much Zavicefta, tell your doctor or nurse straight away. If you have too much Zavicefta it could have an effect on the brain and cause fits or coma.

**If you miss a dose of Zavicefta**
If you think you have missed a dose, tell your doctor or nurse straight away.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

### 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

**Serious side effects**
Tell your doctor straight away if you notice any of the following serious side effects - you may need urgent medical treatment:
- severe allergic reactions – signs include sudden swelling of your lips, face, throat or tongue, a severe rash or other severe skin reactions, difficulty swallowing or breathing. This reaction may be life-threatening.
- diarrhoea that keeps getting worse or does not go away, or stools that contains blood or mucus – this may happen during or after treatment is stopped with Zavicefta. If this happens do not take medicines that stop or slow bowel movement.

Tell your doctor straight away if you notice any of the serious side effects above.

**Other side effects**
Tell your doctor or nurse if you notice any of the following side effects:

**Very common:** (may affect more than 1 in 10 people)
- abnormal result with a test called “DAGT” or “Coombs”. This test looks for antibodies that fight against your red blood cells. It is possible that this could cause anaemia (which may make you feel tired) and jaundice (yellowing of the skin and eyes)

**Common:** (may affect up to 1 in 10 people)
- fungal infections, including those of the mouth and vagina
- change in the number of some types of blood cells (called “eosinophils” and “thrombocytes”) – shown in blood tests
- headache
- feeling dizzy
- feeling sick (nausea) or being sick (vomiting)
- stomach pain
- diarrhoea
- increase in the amount of some enzymes produced by your liver - shown in blood tests
• raised itchy skin rash (“hives”)
• itchiness
• redness, pain or swelling where Zavicefta was given into a vein
• fever

**Uncommon:** (may affect up to 1 in 100 people)
• increase in the number of a type of blood cell (called “lymphocytes”) – shown in blood tests
• decrease in the number of some types of blood cells (called “leucocytes”) - shown in blood tests
• tingling or numbness
• bad taste in your mouth
• an increase in the level of some types of substances in your blood (called “creatinine” and “urea”). These show how well your kidneys are working.

**Very rare:** (may affect up to 1 in 10,000 people)
• swelling in a part of the kidney that causes a reduction in its normal working function

**Not known:** (frequency cannot be estimated from the available data)
• significant decrease in the type of white blood cells used to fight infection - shown in blood tests
• decrease in the number of red blood cells (haemolytic anaemia) – shown in blood tests
• severe allergic reaction (see **Serious side effects**, above)
• yellowing of the whites of the eyes or skin
• sudden onset of a severe rash or blistering or peeling skin, possibly accompanied by a high fever or joint pain (these may be signs of more serious medical conditions such as toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme or a condition known as DRESS, Drug Reaction with Eosinophilia and Systemic Symptoms)
• swelling under the skin, particularly lips and around the eyes

Tell your doctor or nurse if you notice any of the side effects listed above.

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

5. **How to store Zavicefta**

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

Do not use this medicine after the expiry date which is stated on the container. The expiry date refers to the last day of that month.

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

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

6. **Contents of the pack and other information**

**What Zavicefta contains**
• The active substances are ceftazidime and avibactam. Each vial contains ceftazidime pentahydrate equivalent to 2 g ceftazidime and avibactam sodium equivalent to 0.5 g avibactam.
The other ingredient is sodium carbonate (anhydrous).

What Zavicefta looks like and contents of the pack
Zavicefta is a white to yellow powder for concentrate for solution for infusion in a vial. It is available in packs containing 10 vials.

Marketing Authorisation Holder
Pfizer Ireland Pharmaceuticals
Operations Services Group
Ringaskiddy, County Cork
Ireland

Manufacturer
GlaxoSmithKline Manufacturing S.p.A. Via Alessandro Fleming 2
Verona 37135
Italy

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

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Tél: +33 (0)1 58 07 34 40

Portugal
Laboratórios Pfizer, Lda.
Tel: +351 21 423 5500
The following information is intended for healthcare professionals only:

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

Aseptic technique must be followed in preparing the infusion solution. The contents of Zavicefta vial should be reconstituted with 10 mL of sterile water for injections. Instructions for the reconstitution of Zavicefta vial are summarized below:

<table>
<thead>
<tr>
<th>Dosage strength ceftazidime/avibactam (mg)</th>
<th>Volume of diluent to be added (mL)</th>
<th>Approximate ceftazidime/avibactam concentration (mg/mL)</th>
<th>Amount to be withdrawn</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000/500</td>
<td>10</td>
<td>167.3/41.8</td>
<td>Total volume</td>
</tr>
</tbody>
</table>

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.

The reconstituted solution must be further diluted to produce Zavicefta solution for infusion. A 100 mL infusion bag can be used to prepare the infusion, based on the patient’s volume requirements. Appropriate infusion diluents include: 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. The resulting solution should be administered over 120 minutes.

Reconstitution time is less than 2 minutes. Mix gently to reconstitute and check to see that the contents have dissolved completely. The total time interval between starting reconstitution and completing preparation of the intravenous infusion should not exceed 30 minutes. Parenteral medicinal products should be inspected visually for particulate matter prior to administration.

The colour of Zavicefta infusion solution is pale yellow and free of particles.

Studies have shown that Zavicefta solutions for infusion are stable for up to 12 hours at room temperature. Alternatively they are stable for up to 24 hours under refrigerated storage. Once removed from refrigeration to room temperature, the diluted product must be used within 12 hours. The total in-use stability from reconstitution to administration should not exceed 36 hours (24 hours at 2-8°C plus 12 hours room temperature).

From a microbiological point of view, the medicinal product should be used immediately unless reconstitution and dilution has taken place in controlled and validated aseptic conditions. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

The compatibility of Zavicefta with other medicines has not been established. Zavicefta should not be mixed with or physically added to solutions containing other medicinal products.

Each vial is for single use only.

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