EMBLAVEO® (AZTREONAM-AVIBACTAM)

RISK MANAGEMENT PLAN

RMP Version number: 1.0

Data lock point for this RMP: 28 June 2023

Date of final sign off: 12 March 2024

Rationale for submitting an updated RMP: The Applicant is submitting an updated RMP upversion 1.0 for the CHMP adoption and to respond to the Second CHMP & PRAC Joint Assessment Reports and D136 PI comments dated 08 March 2024 as part of procedure EMEA/H/C/006113/0000.

Summary of significant changes in this RMP:

Table 1. RMP Summary of Changes

RMP Part/Module	RMP v 0.3 Main Changes
PART I PRODUCT(S) OVERVIEW	
	No changes
PART II SAFETY SPECIFICATION	
PART II.Module SI Epidemiology of the Indication(s) and Target Population (s)	No changes
PART II.Module SII Non-Clinical Part of the Safety Specification	No changes
PART II.Module SIII Clinical Trial Exposure	No changes
PART II.Module SIV Populations Not Studied in Clinical Trials	No changes
PART II.Module SIV Post-Authorisation Experience	No changes
PART II.Module SVI Additional EU Requirements for the Safety Specification	No changes
PART II.Module SVII Identified and Potential Risks	No changes
PART II.Module SVIII Summary of the Safety Concerns	No changes
PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)PART III	
III.1 Routine Pharmacovigilance Activities	No changes
III.2 Additional Pharmacovigilance Activities	No changes
PART IV PLANS FOR POST AUTHORISATION EFFICACY STUDIES	
	No changes
PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	
	No changes
PART VI SUMMARY OF THE RISK MANAGEMENT PLAN	

Table 1. RMP Summary of Changes

RMP Part/Module	RMP v 0.3 Main Changes
	No changes
PART VII ANNEXES TO THE RISK MANAGEMENT PLAN	
	As per the Second CHMP & PRAC Joint Assessment Reports and D136 PI comments, Annex 1 (EudraVigilance Interface) has been included in the RMP body.
	Annex 8: updated to reflect the changes overtime

Other RMP versions under evaluation:

None

QPPV name[1]: Barbara De Bernardi

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

[1] QPPV name will not be redacted in case of an access to documents request; see HMA/EMA Guidance document on the identification of commercially confidential information and personal data within the structure of the marketing-authorisation application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

ACH	Acute care hospital
ADR	Adverse Drug Reaction
AER	Adverse Event Report
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
ATM-AVI	Aztreonam-Avibactam
AUC	Area under the Curve
BAT	Best available therapy
BLI	β lactamase inhibitor
BSI	Bloodstream Infection
CDAD	*Clostridioides* difficile-associated diarrhoea
CDS	Core Data Sheet
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
cIAI	Complicated Intra-Abdominal Infections
CIAOW	Complicated Intra-Abdominal Infections Worldwide Observational
Cmax	Maximum concentration
COL	Colistin
COPD	Chronic obstructive pulmonary disease
CrCl	Creatinine clearance
CRRT	Continuous renal replacement therapy
CSP	Core Safety Profile
cUTI	Complicated Urinary Tract Infections
DLP	Data-Lock Point
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EEIG	European Economic Interest Group
EMA	European Medicines Agency
EPAR	European public assessment report
ESBLs	Extended-spectrum β-lactamases
EU/EAA	European Union and European Economic Area
FDA	(US) Food and Drug Administration
HA	Health Authority
HAIs	Healthcare-associated infections
HAP	Hospital Acquired Pneumonia
HIV	Human immunodeficiency virus
HLT	High Level Term
IBD	International Birth Date
ICU	Intensive care unit
IQR	Interquartile range
KPC	*Klebsiella pneumoniae* carbapenemase
LLT	Lowest Level Term
LoQs	List of questions

LTCF	Long-term care facilities
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
MBL	Metallo-β-lactamase
MDR	Multi-drug resistance
MedDRA	Medical Dictionary for Regulatory Activities
MER	Meropenem
MRHD	Maximum Recommended Human Dose
MTZ	Metronidazole
NA	Not applicable
NHS	National Health Service
NOAEL	No-observed-adverse-effect level
NP	Nosocomial pneumonia
PBPs	Penicillin binding proteins
pH	Potential of hydrogen
PK	Pharmacokinetic
PT	Preferred Term
RSI	Reference Safety Information
SAE	Serious Adverse Event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
UK	United Kingdom
US	United States
UTI	Urinary Tract Infections
VAP	Ventilator Associated Pneumonia

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Aztreonam-Avibactam (ATM-AVI)
Pharmacotherapeutic group(s) (ATC Code)	Antibacterials for systemic use (ATC code not yet available)
Marketing Authorisation Applicant	Pfizer Europe MA EEIG
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	EMBLAVEO®
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class: Antibacterials for systemic use, other beta-lactam antibacterials, monobactams.
	Summary of mode of action: Emblaveo® is a fixed ratio (3:1) combination of the monobactam antibiotic aztreonam (ATM) and the β-lactamase inhibitor avibactam (AVI). Aztreonam inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin binding proteins (PBPs), which leads to bacterial cell lysis and death and is stable to class B enzymes (metallo β-lactamases) but susceptible to serine β-lactamase. Avibactam is a non β-lactam, β-lactamase inhibitor that acts by forming a covalent adduct with the enzyme that is stable to hydrolysis. Avibactam inhibits both Ambler class A and class C β-lactamases and some class D enzymes, including extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase (KPC) and OXA-48 carbapenemases, and AmpC enzymes. Avibactam does not inhibit class B enzymes and is not able to inhibit many class D enzymes.
	Important information about its composition - The active substances are aztreonam and avibactam. Each vial contains 1.5 g aztreonam and avibactam sodium equivalent to 0.5 g avibactam.

<table>
<tr><td></td><td>- The other ingredients are L-Arginine and Sodium.</td></tr>
<tr><td>Hyperlink to the Product Information:</td><td>Please refer to Module 1.3.1 of this submission.</td></tr>
<tr><td>Indication(s) in the EEA</td><td>Current:

Emblaveo® is indicated for the treatment of the following infections in adult patients:

• Complicated intra-abdominal infection (cIAI)

• Hospital-acquired pneumonia (HAP) including ventilator associated pneumonia (VAP)

• Complicated urinary tract infection (cUTI), including pyelonephritis

Emblaveo® is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults patients with limited treatment options.</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:

Dose in adults with estimated creatinine clearance (CrCL) >50 mL/min

Table 2 shows the recommended intravenous dose for patients with a creatinine clearance (CrCL) > 50 mL/min. A single loading dose is followed by maintenance doses beginning at the next dosing interval.

Table 2. Intravenous dose of Emblaveo by type of infection in adult patients with CrCL > 50 mL/min

<table><tr><th rowspan="2">Type of infection</th><th colspan="2">Dose of aztreonam avibactam</th><th rowspan="2">Infusion time</th><th rowspan="2">Dosing interval</th><th rowspan="2">Duration of treatment</th></tr><tr><th>Loading</th><th>Maintenance</th></tr><tr><td>cIAI</td><td>2 g/ 0.67 g</td><td>1.5 g/0.5 g</td><td>3 hours</td><td>Every 6 hours</td><td>5-10 days</td></tr><tr><td>HAP, including VAP</td><td>2 g/ 0.67 g</td><td>1.5 g/0.5 g</td><td>3 hours</td><td>Every 6 hours</td><td>7-14 days</td></tr><tr><td>cUTI, including pyelonephritis</td><td>2 g /0.67 g</td><td>1.5 g/0.5 g</td><td>3 hours</td><td>Every 6 hours</td><td>5-10 days</td></tr><tr><td>Infections due to aerobic Gram-negative organisms in patients with limited treatment options</td><td>2 g/ 0.67 g</td><td>1.5 g/0.5 g</td><td>3 hours</td><td>Every 6 hours</td><td>Duration in accordance with the site of infection and may continue for up to 14 days</td></tr></table>

Special populations: refer to SmPC section 4.2</td></tr>
</table>

Pharmaceutical form(s) and strengths	Current: Emblaveo® will be available as powder for concentrate for solution for infusion (10 vials). Each vial contains 1.5 g aztreonam and avibactam sodium equivalent to 0.5 g avibactam.
Is/will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Aztreonam-Avibactam (ATM-AVI) is indicated in adult patients for the treatment of the following infections:

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

ATM-AVI is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults patients with limited treatment options.

Infections caused by Gram-negative bacteria are becoming increasingly prevalent worldwide with the majority of infections being nosocomial infections.[1,2] Estimates for the United States (US) indicate that 648,000 patients a year acquire infections while in the hospital (nosocomial infections)[3] and data from Europe suggest that 3.8 million patients acquire nosocomial infections per year.[4]

The increasing prevalence of antimicrobial resistance in Gram-negative bacteria is becoming a threat to public health worldwide.[2] According to data from the European Center of Disease and Control (ECDC), antibiotic-resistant bacteria caused 600,000 infections and 27,000 attributable deaths in 2015 in Europe with 70% of the disease burden caused by multi-drug-resistant Gram-negative bacteria.[5] In the US, antibiotic-resistant bacteria were estimated to cause more than 2.8 million infections and at least 35,000 associated deaths per year.[6]

Enterobacterales resistant to carbapenems by producing metallo enzymes (metallo-β-lactamases, MBL) have become more prevalent in clinical settings worldwide.[7,8] In the USA, a study in which the activity of aztreonam-avibactam and comparators were evaluated against *Enterobacterales* isolates collected from 74 US medical centers in 2019–2021 (N=9686 in 2019; N=8916 in 2021) showed as a percentage of all carbapenem-resistant enterobacterales (N=80; 97, respectively), the frequencies of MBL producers increased markedly from 3.8% (n=3) in 2019 to 20.4% (n=20) in 2021.[9] MBL-producing pathogens have also been reported throughout Europe and Asia-Pacific, with outbreaks noted in several countries.[10]

In particular, existing treatment options for Gram-negative infections caused by pathogens expressing MBL have safety and tolerability concerns such as nephrotoxicity (colistin), all cause-mortality (tigecycline; cefiderocol) and antimicrobial resistance. Inappropriate use of antibacterial agents presents poor antimicrobial stewardship and increases the risk of antimicrobial resistance.Considering that Gram-negative bacteria can cause infections throughout the body, this section focuses on an epidemiologic review of the most common and severe forms of infections caused by Gram-negative bacteria[2] including cIAI, HAP including VAP, and cUTI including pyelonephritis.

SI.1. Complicated Intra-Abdominal Infections (cIAI)

cIAI include a wide spectrum of pathological conditions: intra-abdominal abscess, perforated appendicitis, perforated diverticulitis, complicated by abscess formation or faecal contamination, cholecystitis with evidence of perforation or empyema, intestinal perforation with abscess formation or faecal contamination, peritonitis, gastric or duodenal ulcer perforation, and traumatic bowel perforation. In cIAI, the infection proceeds beyond a single organ and causes other localized peritonitis (intra-abdominal abscesses) or diffuse peritonitis.[11]

Incidence:

cIAI are highly diverse in their aetiology, clinical manifestations, and severity. The overall incidence and prevalence of cIAI in the general population was not available from the literature; rates of specific types of cIAI are presented in the section instead.

A study describing the epidemiology of peptic ulcers in a region of Denmark using population based registers between 1993 and 2002 reported an incidence of 0.8 cases of perforated peptic ulcer per 10,000 person-years (95% CI 0.6-1.1) in 2002.[12] This was a statistically significant decrease since 1993, when the incidence was 1.4 per 10,000 person-years (95% CI 1.1-1.8).[12]

The Scottish Morbidity Records database covers all non-obstetric and non-psychiatric discharges from NHS hospitals in Scotland. In 2000-2002, the overall incidence of perforated gastric or peptic ulcer was 0.22 per 10,000 persons per year among men and 0.23 per 10,000 per year among women.[13] The overall incidence of perforated duodenal ulcer was 1.40 per 10,000 per year among men and 0.83 per 10,000 per year among women. Table 3 provides incidence rates for perforated gastric, peptic, and duodenal ulcers from 2000-2002 in Scotland by gender and age group.[13]

Table 3. Incidence (per 10,000 persons) of Perforated Gastric, Peptic, and Duodenal Ulcer in Scotland, 2000-2002, by Gender and Age Group

		25-44 years	45-64 years	65-74 years	75 + years
Men	Perforated gastric or peptic ulcer	0.15	0.30	0.70	1.08
	Perforated duodenal ulcer	0.80	2.02	4.65	6.51
Women	Perforated gastric or peptic ulcer	0.13	0.42	0.51	1.22
	Perforated duodenal ulcer	0.45	1.13	2.78	5.39

In 5 hospitals in the UK, during 1995-2002, the adult age-adjusted (adjusted to the UK population) incidence of acute perforated colonic diverticular disease was 0.35 per 10,000 per year. In both sexes, incidence increased with age.[14]

In the US, appendicitis is a common condition. Based on a retrospective analysis of a database of all patients treated at acute care hospitals in California, the incidence of appendicitis was 2.96 cases per 10,000 in the last quarter of 2009.[15] The cumulative lifetime risk of appendicitis for people aged 85 and older was 9.0%. Among 608,116 observed appendicitis cases, perforated appendicitis accounted for 29.7% of cases.[15]

According to the global burden of disease study in 2019, the age-standardized incidence rate of appendicitis was 229.9 events per 100,000 population globally; on the regional level, the age-standardized incidence rates of appendicitis per 100,000 population were 220.3 in central Europe, 273.2 in eastern Europe, 278.5 in western Europe, and 162.6 in North America.[16]

Prevalence:

In a multicentre observational study conducted from October 2012 to March 2013 across 68 medical institutions worldwide (Complicated Intra-Abdominal Infections Worldwide Observational Study [CIAOW study]), 1,898 patients were followed and treated for cIAI.[17] A total of 86.7% (n=1,645) of patients were affected by community-acquired IAIs, and 13.3% (n=253) suffered from HAIs. Generalised peritonitis was experienced by 43.6% (n=827) of patients, and 56.4% (n=1,071) of patients suffered from localised peritonitis or abscesses.

The most common infection source was appendicitis (33.3%), followed by cholecystitis (14.6%), gastrointestinal perforations (13.3%), post-operative infection (8.9%), small bowel perforation (7.6%), others (6.4%), colonic non-diverticular perforation (6.1%), diverticulitis (5.6%), post traumatic perforation (2.4%), and pelvic inflammatory disease (1.6%). The major pathogens involved were *Enterobacteriaceae*.[17]

According to the global burden of disease study in 2019, the age-standardized prevalence of appendicitis was 8.7 per 100,000 population globally; on the regional level, the age-standardized prevalence of appendicitis per 100,000 population were 8.4 in central Europe, 10.4 in eastern Europe, 10.6 in western Europe, and 6.2 in North America.[16]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

In the CIAOW study that included 1,898 patients, the mean age was 51.6 years (range 18-99 years); 41% were women and 59% were men.[17] In a pooled study from five European observational studies that included 785 cIAI patients who receiving tigecycline treatment,[18] the mean age was 63.1 (SD, 14) and 58.2% were men.

Specifically, inherent and acquired risk factors include anatomical abnormalities of the abdomen, male gender, older age (>70 years), diabetes mellitus, renal insufficiency, abdominal tumours, diverticula, healthcare-associated infection, immunocompromised state (pulmonary disease, liver disease, and transplantation), prior antimicrobial exposure, high degree of intra-abdominal contamination, severe sepsis, septic shock, malignancy, serious cardiovascular disease, poor nutritional state, low albumin levels, recent antibiotic use, and organ failure.[17,19-21]

The main existing treatment options:

The management of cIAI involves both the use of antibiotics and surgical intervention. Both treatment options should be commenced promptly upon a definitive or presumed diagnosis of cIAI. Antibiotics should be commenced on diagnosis and before surgery and continued after surgery. The aim of the surgery or non-surgical intervention is to achieve source control (eg., drainage of any infection and repair of any defects that caused the infection). The type and extent of surgery will depend upon the nature of the cIAI.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality

Mortality rates vary according to the source of infection: 0.25% to 9% for the appendix and much higher rates for the stomach/duodenum (21%), pancreas (31%), small bowel (38%), large bowel (45%), and biliary tract (50%).[22-24]

The CIAOW study reported an overall mortality rate of 10.5% (199 of 1,898 patients) among patients with cIAI.[17]

Morbidity

cIAI is amongst the most common infections with high morbidity as patients may have multiple comorbidities, may be at risk for treatment failure, and are sometimes septic before they are diagnosed.[25,26] Common morbidities include UTI, renal failure, superficial surgical infections, pneumonia, and pulmonary embolism.

Important co-morbidities:

Important co-morbidities are malignancy,[18,27-29] cardiovascular disease,[17,18,29,30] diabetes,[18,29,31] hypertension,[18,31] COPD,[18,29] renal insufficiency,[18,29] and obesity.[18]

SI.2. Hospital Acquired Pneumonia (HAP) including Ventilator Associated Pneumonia (VAP)

HAP (or nosocomial pneumonia [NP]) is defined as pneumonia that occurs 48 hours or more after admission, which was not incubating at the time of admission. VAP is defined as parenchymal lung infection that occurs after at least 48 hours of mechanical ventilation and endotracheal intubation.[32,33]

Incidence:

The global incidence of HAP varies from 5 to more than 20 per 1000 hospital admissions. One-third of HAP cases are considered acquired from intensive care unit (ICU), and the majority of them are VAP.[32,34] The incidence of HAP is highest among immunocompromised, surgical and older patients.[34] In the US, the estimated incidence of VAP ranges from 2 to 6 cases per 1000 ventilator-days, and incidence of non-ventilator HAP is 3.63 per 1000 patient-days.[35]

The average of length of stay for patients with VAP (n=3,420) was 28.4 days whereas the length of stay was 13.1 days for patients with non-ventilator HAP (n=119,075).[35] In another large surveillance study using electronic health record data from 284 US hospitals, the incidence of non-ventilator HAP was 0.55 events per 100 admissions or 0.96 events per 1000 patient-days; the median length of stay for patients with non-ventilator HAP was 16 (interquartile range: 11-26) days.[36] The incidence of VAP in Europe appears much higher in ICU patients, exceeding 18 per 1000 ventilator-days.[37]

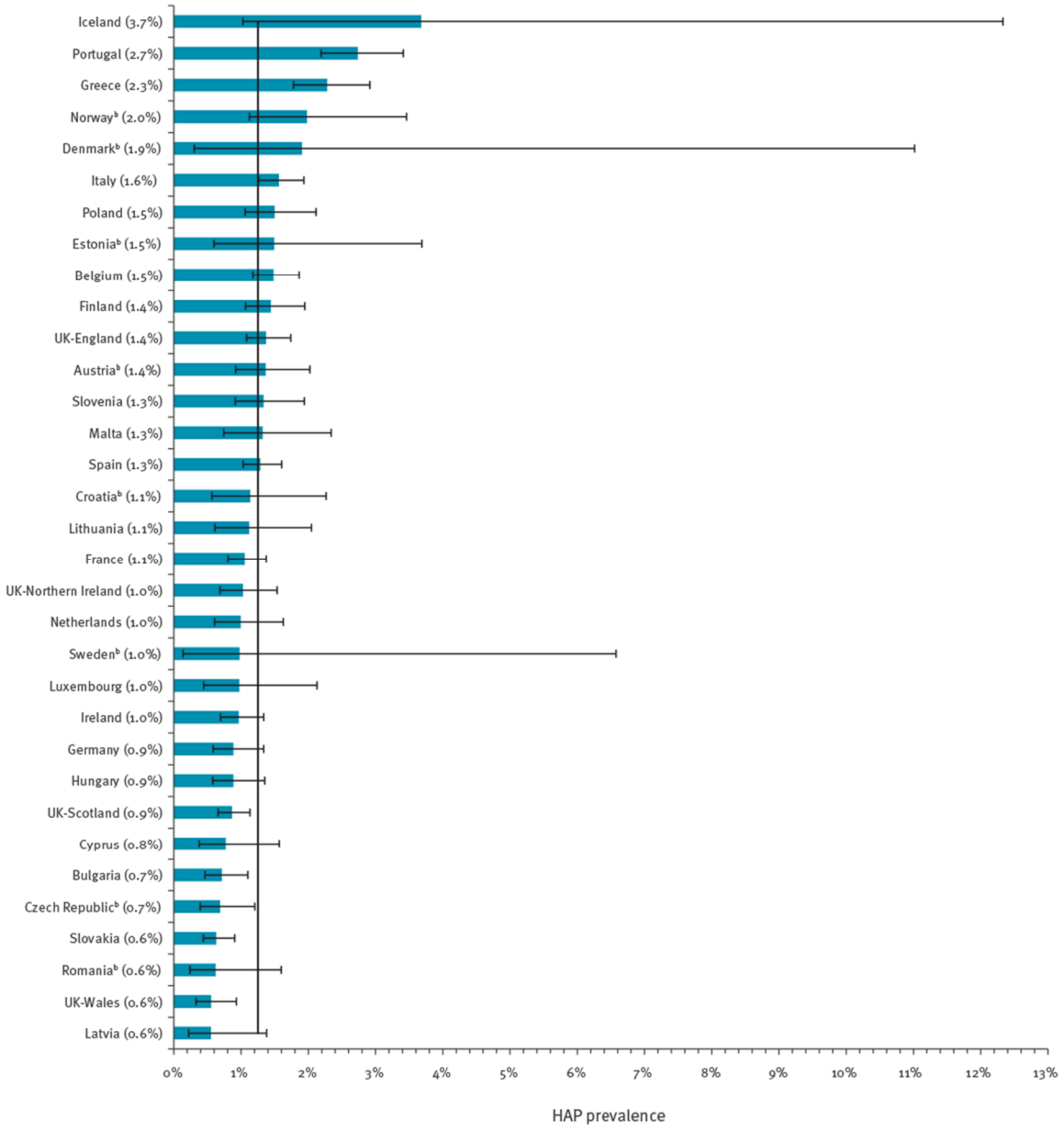
In general, the large variation in reported incidence rates of HAP and VAP can be attributed to factors such as variations in case definition, data source, and the population evaluated by each study.[32]

Prevalence:

Prevalence of HAP in Europe:
A point prevalence survey of healthcare-associated infections (HAIs) was conducted by ECDC from 2016 to 2017 including 310,755 patients from 1,209 acute care hospitals (ACH) in 28 European Union and European Economic Area (EU/EEA) countries and 117,138 residents from 2,221 long-term care facilities (LTCF) from 23 EU/EEA countries.[4] HAP was present in 4,200 patients, accounting for 21.4% of all HAIs and resulting in a country-weighted prevalence of 1.26% (95% CI: 0.96–1.68) on any given day among hospitalised patients in ACH in Europe. After correction for non-participating countries, 862,000 (95% CI, 568,000 – 1,283,000) episodes of HAPs were estimated to occur each year in European ACH.[4]

An earlier point prevalence survey conducted from 2011 to 2012 reported a similar prevalence (1.3%; 95% CI, 1.2–1.3; n=2,902) of HAP on any given day among hospitalized patients across Europe. Patients with long hospital stay, old age and men had a high prevalence of HAP. The prevalence of HAP varied from 0.6% (95% CI, 0.2–1.4) in Latvia to 3.7% (95% CI, 1.0–12.3) in Iceland. (Figure 1)[38]

Figure 1. Prevalence of HAP, ECDC Point Prevalence Survey in ACH in EU/EEA, 2011–2012 (n = 231,459 patients)



Source: Walter et al, 2018

Prevalence of HAP in the US

Two multistate point-prevalence surveys have been conducted to estimate the prevalence of HAIs using the National Healthcare Safety Network criteria. The 2011 survey was conducted among 183 hospitals from 10 diverse states with 11,282 patient participants, of which 452 had 1 or more HAIs. In 2015, a total of 12,299 patients in 199 hospitals from the same 10 states were surveyed.

Results from two multistate point-prevalence surveys suggest that non-ventilator HAP and VAP combined were the most common type of HAIs and accounted for 21.8% (n=110) of all HAIs in the US during 2011[3] and 25.8% (n=110) in 2015.[39]

In 2011, the estimated number of infections was 157,500 (95% CI, 50,800-281,400), with 60.9% of these classified as non-ventilator HAP.[3] In 2015, the estimated prevalence of non-ventilator HAP and VAP combined was 0.89% (95% CI, 0.74-1.10) and the prevalence of VAP was 0.32% (95% CI, 0.23-0.43).[39]

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Data from 2012 US National Inpatient Sample suggest that patients with non-ventilator HAP (n=119,075) had a mean age of 67.0 years with 52% men and patients with VAP (n=3,420) had a mean age of 58.2 years with 63% men.[35]

Results from a large multicentre retrospective cohort study using US hospital data from 2012-2019 suggest that patients with non-ventilator HAP (n=4,728) had a mean age of 66.7 years (SD, 15.1) with 76.2% White and 60.2% males. Patients with VAP (n=8,530) had a mean age of 59.7 years (SD, 16.6) with 70.3% White and 65.2% males.[40] The proportions of Black and Hispanic in non-ventilator HAP patients were 12.7% and 3.3%, respectively, and 17.7% and 3.9%, respectively, among VAP patients.[40]

Risk factors associated with HAP are summarised in Table 4 below.

Table 4. Risk Factors for the Development of HAP

Host factors	Environmental factors	Pharmacologic factors
Colonisation of the digestive and upper respiratory tract with pathogenic microorganisms Previous treatment with broad-spectrum antibiotic Renal dysfunction Coma Shock Diabetes Uraemia Chronic obstructive pulmonary disease Hypoalbuminaemia Advanced age Underlying lung disease Surgery Intubation Mechanical ventilation Male gender ICU admission for trauma Intermediate underlying Disease severity Tracheotomy Enteral feeding	Increased gastroesophageal reflux of stagnant oral secretions as a result of indwelling nasogastric tubes Concomitant sinusitis Movement of ICU Patients from the ICU for surgical and diagnostic procedures	Gastric bacterial colonisation can lead to contamination of tubing, which can correlate with non-acidic gastric pH; drugs affecting the pH have an impact on risk Use of paralytic agents

ICU = Intensive Care Unit; Source[41,42]

The main existing treatment options:

The treatment recommendations for HAP depend on the timing of the onset of pneumonia and the presence of additional risk factors. The recommended duration of pharmacologic treatment is 8 days but is subject to variation based on aetiology.[43] However, patients with NP due to *P. aeruginosa* may require longer drug administration ranging from 14 to 21 days.[32,44,45]

Table 5 below summarises the antibiotics recommended in the empirical management of HAP.[46]

Table 5. Antibiotics Recommended in the Empirical Management of HAP due to Gram-Negative Infections

Length of hospital stay	Recommended antibiotic therapy
<5 days before the development of pneumonia.	Ceftriaxone, ampicillin–sulbactam, levofloxacin, moxifloxacin, ertapenem.
≥5 days before the development of pneumonia or the diagnosis of HAP.	Anti-pseudomonal β-lactam regimens: cefepime; ceftazidime; piperacillin-tazobactam; ticarcillin clavulanate; meropenem; imipenem; doripenem; aztreonam with ciprofloxacin, levofloxacin, gentamicin, or tobramycin; or amikacin.

Guidance on the treatment of NP based on a task force of scientific personnel from 3 European Societies: the European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and European Society of Intensive Care Medicine has been published.[47] In general, immediate administration of appropriate antimicrobial treatment is important for an optimal outcome. Adequate dosing is important in order to have a favourable outcome.[47]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Mortality

Globally, HAP and VAP are considered the leading cause of death due to nosocomial infections.[48] The estimated global mortality due to HAP is 20-30% and the mortality due to VAP is 20-50%.[48]

In the US, the in-hospital mortality for patients with VAP was 19.4 -21.3% and the in-hospital mortality for patients with non-ventilator HAP was 11.7-13.1%.[35,40] VAP was associated with higher risk of mortality compared to non-ventilator HAP after adjusting for patient demographics and clinical variables (odds ratio, 1.71; 95% CI, 1.56-1.87).[35] In another large study in the US using electronic surveillance criteria, the crude inpatient mortality was 22.4% for patients with non-ventilator HAP.[36]

A prospective multicenter study in central Europe identified 201 patients with HAP, of which 79.1% (n=159) of patients had VAP. The 30-day mortality for patients VAP and non-ventilator HAP was 34.6% and 12.7%, respectively.[49]

Important co-morbidities:

Important co-morbidities are cardiac disorders,[50] pulmonary disorders,[40,51] nephrotoxicity/renal dysfunction,[40,52-56] congestive heart failure,[40] neurological disorders,[40] diabetes,[40] liver disease,[40] coagulopathy,[40] cancer,[40] depression,[40] and hypertension.[40]

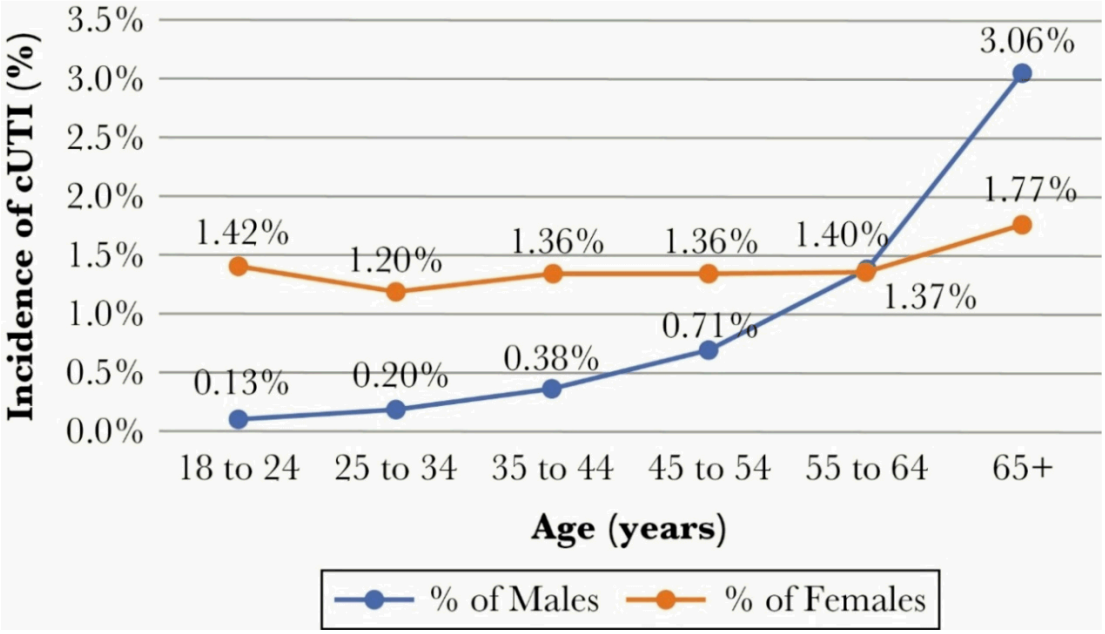
SI.3. Complicated Urinary Tract Infections (cUTI) Including Pyelonephritis

UTI is a bacterial infection of predominantly the lower organs (acute cystitis) or, more rarely, the upper renal pelvis and kidney (acute pyelonephritis).[57] UTI can be categorized as community-acquired, hospital-acquired or healthcare-associated infections.[58] cUTI denotes those cases complicated with an intrinsic or extrinsic functional or structural abnormality of the genitourinary tract, and/or those with significant medical or surgical comorbidities.[59-61] Some investigators consider any UTI in patients more than 65 years of age or in men at any age to be a cUTI.[61,62] The US Food and Drug Administration (FDA) considers pyelonephritis a cUTI even in the absence of other complicating factors.

Incidence:

A large retrospective study conducted using US claims data from 2013 to 2017 reported an incidence rate of 4.9 cases per 1000 person years. The estimated annual incidence of cUTI is 1.14% among US adults, equating to over 2.8 million cases of cUTI per year.[63] Women have a higher incidence of cUTI than men until age 55. In patients aged ≥ 65, men's incidence of cUTI exceeds women's rate (Figure 2).

Figure 2. Incidence of cUTI by Age and Sex



Source, Carreno et al 2020[63]

The incidence of cUTI in Europe were not available in the literature. However, incidence of UTIs in general has been reported increasing with age in both sexes: the incidence of UTIs increased from 12-29 cases per 100 person-years in community-dwelling elders (8-12 per 100 person-years amongst men and 13-29 per 100 person-years amongst women) to 44-58 cases per 100 person-years in LTCF (precise age range not specified and assumed to be complicated based on age and setting).[64]

Data from a Dutch cohort (the Leiden 85-plus Study) indicated that the incidence of UTIs was 11.2 cases per 100 person-years (95% CI: 9.4, 13.1) among 479 patients aged 86 years.[64]

Prevalence:

Prevalence of cUTI was not identified from the literature but the prevalence of healthcare-associated UTI has been reported from point prevalence surveys in Europe and the US.

Prevalence of healthcare-associated UTI in Europe:

UTI was present in 3,710 patients, accounting for 18.9% of all HAIs and resulting in a country-weighted prevalence of 1.10% (95% CI: 0.85–1.43) on any given day among hospitalised patients in ACH in Europe. After correction for non-participating countries, 870,000 (95% CI, 572,000 – 1,279,000) episodes of UTI were estimated to occur each year in European ACH.[4] In contrast, in terms of UTI originated from LTCF, UTI was present in 1,233 patients, accounting for 32% of all HAIs and resulting in a country-weighted prevalence of 1.29% (95% CI: 0.87–1.66) on any given day among patients in LTCF in Europe. After correction for non-participating countries, about 1.3 million episodes UTI were estimated to occur each year in European LTCF.[4]

Prevalence of healthcare-associated UTI in the US:

In the 2015 US point prevalence survey, UTI was present in 39 patients, accounting for 9% of all HAIs, which was equivalent to a US prevalence of 0.32% (95% CI: 0.23–0.43%) on any given day among hospitalised patients admitted for all-causes in ACH in 2015.[39] Data from the 2011 US point prevalence survey suggest that the estimated number of healthcare-associated UTI infections in 2011 was 93,300 (95% CI, 28,100-311,800).[3]

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

cUTI can occur in any age group but are more common among those aged >60 years. The mean age reported in 2 European observational studies conducted among patients with cUTI was 62 years.[59,65] cUTI occurs in both sexes; however, they have been reported more frequently among females compared with males until the age of 60 years. Any UTI among males is usually considered as cUTI because uncomplicated UTI is rare in men.[61] In previously conducted clinical and observational studies among patients with cUTI, the proportion of males reported has ranged from 38% to 78%.[59,65,66]

Catheter, particularly the duration of catheterisation, is a major risk factor for hospital-acquired UTI.[67] In an observational study conducted among patients with cUTI, 17% of patients had the presence of a urinary catheter.[65] However, the incidence of catheter-associated UTI varies considerably by region and treating unit within the hospital (ranging 0.50 to 15 per 1000 catheter-days).[68]

Other risk factors related to cUTI can be broadly classified into structural and functional abnormalities.[61,69,70]

Obstruction due to stones or tumors in any part of the urinary tract, prostatic hypertrophy, or congenital abnormalities causing impeded flow have been associated with increased risk of UTI. Similarly, functional abnormalities such as impaired and/or incomplete voiding due to neurological conditions, neuropathic bladder, or vesicoureteral reflux are also related to increased risk of UTI. Interventional risk factors for cUTI include recent antibiotic use, indwelling catheters, ureteric stents or splits, obstruction of nephrostomy tubes, surgery, and valves.[62,71]

Finally, other factors making UTI cases complicated, either through contributing to impaired urine flow or through altering response to antibiotic therapy, include male gender, diabetes, pregnancy, and immunosuppressed state.[70,72]

The main existing treatment options:

Obstruction or anatomic abnormalities, if any, are addressed first, followed by aggressive administration of broad-spectrum antibiotics to cover both Gram-positive and Gram-negative bacteria. A fluoroquinolone with mainly renal excretion, an aminopenicillin with a β lactamase inhibitor (BLI), a Group 2 or 3a cephalosporin, and an aminoglycoside (for parenteral therapy) are recommended options. If first-line treatment fails, or in cases of clinically severe infections, a broader-spectrum antibiotic should be chosen that is also active against *P. aeruginosa* (eg., a fluoroquinolone [if not already used], an acylaminopenicillin with a BLI, a Group 3b cephalosporin, or a carbapenem with or without an aminoglycoside).[73] The choice of antibiotic treatment depends on the pathogen and local susceptibility patterns.

Additionally, the risk of multi-drug-resistant infections due to factors such as prior recent hospitalisation or recent antibiotic use should be accounted for prior to the selection of antibiotic therapy. Finally, severe cUTI cases may require hospitalisation for appropriate management.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

<u>Mortality</u>

Results from a multinational retrospective cohort study conducted in 20 countries in Europe and the Middle East during 2013-2014 reported a 30-day all-cause mortality of 8.7% among 976 hospitalized patients with cUTI.[74] Investigators of another multicenter retrospective cohort study involving 20 hospitals from eight countries from southern Europe, Turkey and Israel found a 30-day mortality of 15.2% among 341 hospitalized patients with catheter-associated UTI and 6% among 466 patients with UTI of other sources.[75] A prospective observational study (n=1,325) conducted among patients with complicated pyelonephritis reported a crude mortality rate of 6.5% and attributable mortality of 4.1%.[76] Finally, in the Leiden 85-plus prospective study conducted in the Netherlands that involved 479 participants aged 86 years old at the beginning of follow-up, 51.4% (n=246) of the participants died during 4-year follow-up, of whom 2.8% (n=7) died due to their cUTI infection.[64]

Morbidity

Although cUTI patients can be asymptomatic, when evident, the clinical presentation varies across a wide spectrum from mild irritative symptoms such as frequency and urgency to unilateral/bilateral loin pain, back pain, and pelvic pain.[61] Fever, rigours, nausea, vomiting, anorexia, and diarrhea may occur with upper UTIs. Recurrent infection and increased antimicrobial resistance are additional risks.[77]

By definition, cUTI involves a subset of patients with more inherent risk (eg., an anatomically abnormal urinary tract or a significant medical comorbidity) or more acquired risk (eg., invasive therapies, modalities, and surgeries) than uncomplicated UTI cases. The profile of cUTI thus includes all the attendant morbidities, costs, and adverse outcome differences due first to complications and second to a longer course of antimicrobial therapy; these are in addition to those expected for UTI.[60] A number of sequelae from cUTI may be serious or fatal. Side effects include urosepsis and shock, hypotension, acute or chronic renal injury/failure, papillary necrosis, renal or perinephric abscess, the development of emphysematous pyelonephritis, and papillary necrosis.[57] Besides suppurative complications, UTI may be associated with bone, joint, or heart tissue infection.[61]

Important co-morbidities:

Important co-morbidities with cUTI (including pyelonephritis) are diabetes[59,60,71,74,78-80], stroke,[81-85], congestive heart failure,[74] dementia,[74] chronic kidney disease,[74] chronic pulmonary disease,[74] cancer,[74] and renal impairment.[74]

Table 6. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Toxicity: • Kidney (cortical tubular vacuolation without effect on renal function was observed at ATM/AVI doses of ≥750/300 mg/kg/day in the 1-month rat study, with no change in renal function)	
• Reproductive/developmental toxicity • No effects on fertility were observed in a study in rats with ATM at doses up to 2400 mg/kg/day • No effects on fertility were observed in a study in rats with doses of AVI up to 1000 mg/kg/day. A slight increase in pre- and post-implantation loss was observed at doses of AVI ≥ 500 mg/kg/day • In a rabbit embryo-foetal development study with AVI, increased post-implantation loss, lower foetal weights, and delayed ossification associated with maternal toxicity • In a pre- and postnatal development study with ATM no effects were observed on development at doses up to 1800 mg/kg/day • In a pre- and postnatal development study with AVI, there were no effects on developmental landmarks at 825 mg/kg/day, the highest dose tested. An increase in renal pelvic and ureter dilatation was observed in the offspring at 450 and 825 mg/kg/day	The available non-clinical data indicate low risk of foetal harm in humans.
• Genotoxicity	None.
• Carcinogenicity	Studies not conducted or required.
• Safety pharmacology	No effects identified.
Other toxicity-related information or data	None.

The toxicology package for ATM-AVI is supported by combination toxicity studies up to 1-month in duration in a single species (rat) that demonstrated AVI did not alter the safety or pharmacokinetic profile of ATM.

Administration of ATM, alone or in a combination with AVI at doses up to 1000/400 mg/kg/day in males and 1500/600 mg/kg/day in females, was associated with non-adverse findings consisting of increases in body-weight gain, food and water consumption, increased plasma triglycerides, decreased plasma creatinine, decreased urinary pH and abnormal coloured urine, higher kidney and liver weights and microscopic changes in the

kidney (cortical tubular vacuolation) and liver (hepatocellular hypertrophy). There was no evidence that AVI altered or contributed to the toxicity of ATM when given in combination. There was evidence of recovery from all ATM-related changes at the end of the 12-week recovery phase, indicating complete reversibility. Higher ATM doses of ≥1500 mg/kg/day in males and 2000 mg/kg/day in females were acutely not tolerated.

The NOAEL for the 1-month GLP combination toxicity study in rats was considered to be 1000/400 mg/kg/day ATM/AVI in males and was associated with a total Cmax of 1850/782 µg/mL ATM/AVI and a total AUC of 2290/894 µg•h/mL ATM/AVI that resulted in exposure margins of 25x/63x for ATM/AVI on a Cmax basis and 1.9x/4.3x on an AUC basis, respectively, based on the exposure projected for the MRHD of ATM/AVI. The NOAEL in females was considered to be 1500/600 mg/kg/day ATM/AVI and was associated with a total Cmax of 2080/918 µg/mL ATM/AVI and a total AUC of 2580/1080 µg•h/mL ATM/AVI that resulted in exposure margins of 28x/74x for ATM/AVI on a Cmax basis and 2.1x/5.2x on an AUC basis, respectively, based on the exposure projected for the MRHD of ATM/AVI.

Considering the established safety profile of ATM and the absence of nonclinical safety concerns for AVI, no genetic or reproductive toxicology studies were conducted for the combination. ATM and AVI are not genotoxic. ATM did not affect fertility, embryo-fetal development, or pre- and post-natal development. AVI did not affect fertility or embryo-fetal development in rats. The NOAEL for embryo-fetal development in rabbits was 100 mg/kg/day resulting in a human exposure margin (AUC) of 1.3x at the MRHD. At higher doses (300 and 1000 mg/kg/day), increased post-implantation loss and/or lower mean fetal weights with delayed ossification of several bones were observed. These AVI-related developmental effects were only noted at maternally toxic doses without evidence of malformations. In a rat pre-and postnatal study up to 825 mg/kg/day IV (6.1x the human exposure based on AUC at MRHD), there were no effects on pup growth and viability. A dose-related increase in the incidence of renal pelvic and ureter dilatation was observed in female weaning pups that was not associated with pathological changes to renal parenchyma or renal function, with renal pelvic dilatation persisting after female weaning pups became adults.

Overall, there were no new or exacerbated toxicological findings in rats when both drugs were administered in combination in comparison to the effects observed from each individual agent. Carcinogenicity studies with ATM-AVI combination were not required or conducted because of the short-term clinical treatment for bacterial infections with ATM-AVI.

Module SIII. Clinical Trial Exposure

The clinical trial exposure data are obtained from three Phase 2/3 studies considered representative of the overall target patient population (ie, patients with serious Gram-negative infections the majority of which were cIAI and HAP/VAP) as per Table 7.

Table 7. Phase 2/3 Studies – Adult population

Study No.	Study Title
C3601002	A Phase 3 prospective, randomized, open-label, central assessor blinded, parallel group, multicenter comparative study to determine the efficacy, safety, and tolerability of ATM-AVI ± MTZ versus MER ± COL for the treatment of serious infections due to Gram-negative bacteria, including MBL-producing MDR pathogens for which there are limited or no treatment options.
C3601009	A Phase 3 prospective, randomized, open-label, parallel group, multicenter comparative study to determine the efficacy, safety, and tolerability of ATM AVI versus BAT for the treatment of serious infections due to Gram-negative, MBL producing MDR pathogens for which there are limited or no treatment options.
C3601001	A Phase 2a prospective, open-label, non-comparative, multicenter study to determine the PK, safety, and tolerability of ATM-AVI in the treatment of hospitalized patients with cIAI.

The Phase 2/3 pool is also supported by data from 3 Phase 1 pooled studies with ATM-AVI treatment arms as per Table 8.

Table 8. Phase 1 Studies – Adult population

Study No.	Study Title
D4910C00001	A Phase 1 double-blind 3-part study to determine the PK, safety and tolerability of ATM-AVI in healthy young and elderly participants.
C3601006	A Phase 1 open-label, parallel group study to determine the PK of ATM-AVI in participants with severe renal impairment and in healthy participants with normal renal function.
C3601007	A Phase 1 open-label, single-center study to determine the PK, safety and tolerability of ATM-AVI in healthy Chinese participants.

There were 409 adult participants (321 from phase 2/3 studies and 88 from Phase 1 studies) exposed to ATM-AVI across the clinical development program:

Study phase	Study No.	No. of Participants
Phase 3	C3601002	275
	C3601009	12
Phase 2a	C3601001	34 (16 from cohort 1 who used a lower maintenance dose of AVI and 18 from both Cohorts 2 and 3 which are included in the Phase 2/3 Safety Pool).
Phase 1	D4910C00001	65 healthy participants.
	C3601006	11 participants, 5 with severe renal impairment.
	C3601007	12 Chinese participants.

The recommended dosing regimen of ATM-AVI is as a loading dose of 2.0 g ATM plus 0.67 g AVI infused over 3 hours, before commencing on a maintenance dose (1.5 g ATM plus 0.5 g AVI) infused over 3 hours every 6 hours. Dose adjustment is required for patients with moderate or severe renal impairment and end stage renal disease.

Exposure data in ATM-AVI clinical studies are summarized below from Table 9 to Table 14.

Table 9. Duration of Exposure to ATM-AVI by Study Phase - Safety Analysis Set

	ATM-AVI (+/-MTZ)* (N=409)	
Duration of Exposure	**Persons**	**Person Time (Days)**
Phase 1 Studies		
1 day	7	7
2-4 days	23	81
5-10 days	21	205
11-14 days	37	407
>14 days	0	0
Total	88	700
Phase 2/3 Studies		
1 day	6	6
2-4 days	26	85
5-10 days	202	1433
11-14 days	56	688
>14 days	31	465
Total	321	2677

Phase 1 pool includes studies C3601006, C3601007 and D4910C00001 (C3601005).
Phase 2/3 pool includes studies C3601002, C3601009 and D4910C00009 (C3601001).
*MTZ therapy administered to participants with cIAI only.
Person-Time (days) represents the cumulative number of days of exposure of the participants represented in the adjacent Persons column.
[redacted] Source Data: adex Table Generation: 28JUN2023 (15:08)
Output File: ./ATM_AVI_Submissions/ATM_AVI_EMA_RMP/adex_exp_all

Table 10. Duration of Exposure to ATM-AVI by Study Doses and by Study Phase - Safety Analysis Set

	ATM-AVI (+/-MTZ)* (N=409)	
Duration of Exposure by Study Doses	**Persons**	**Person Time (Days)**
Phase 1 Studies		
2000 mg ATM/ 667 mg AVI	12	12
2000 mg ATM/ 600 mg AVI	11	45
2000 mg ATM/ 546.7 mg AVI	18	18
2000 mg ATM/ 375 mg AVI	8	88
1500 mg ATM/ 600 mg AVI	8	86
1500 mg ATM/ 500 mg AVI	18	66
1500 mg ATM/ 450 mg AVI	10	110
1500 mg ATM/ 410 mg AVI	28	290
675 mg ATM/ 225 mg AVI	5	15
500 mg ATM/ 167 mg AVI	6	6
Phase 2/3 Studies		
2000 mg ATM/ 667 mg AVI	16	17
2000 mg ATM/ 547 mg AVI	17	19
1500 mg ATM/ 500 mg AVI	297	2402
1500 mg ATM/ 410 mg AVI	17	99
750 mg ATM/ 250 mg AVI	38	143
675 mg ATM/ 225 mg AVI	14	67
500 mg ATM/ 167 mg AVI	276	283
Other*	5	5

Phase 1 pool includes studies C3601006, C3601007 and D4910C00001 (C3601005).
Phase 2/3 pool includes studies C3601002, C3601009 and D4910C00009 (C3601001).
*MTZ therapy administered to participants with cIAI only.
Person-Time (days) represents the cumulative number of days of exposure of the participants represented in the adjacent Persons column.
Study doses include all doses administered to any participants; participants are counted once for each dose level they received during the study and therefore a participant may be in more than 1 exposure group.
* Dose=Other consists of doses 1900 mg ATM/ 633.65 mg AVI, 1500 mg ATM/ 500.25 mg AVI, 750 mg ATM/ 225 mg AVI, 500 mg ATM/ 500 mg AVI, 500 mg ATM/ 250 mg AVI.
[redacted] Source Data: adex Table Generation: 28JUN2023 (15:08)
Output File: ./ATM_AVI_Submissions/ATM_AVI_EMA_RMP/adex_exp_study_doses

Table 11. Duration of Exposure to ATM-AVI by Age Group, by Gender and by Study Phase - Safety Analysis Set

	ATM-AVI (+/-MTZ)* (N=409)					
	Female		Male		Total	
Age Group (Years)	Persons	Person Time (Days)	Persons	Person Time (Days)	Persons	Person Time (Days)
Phase 1 Studies						
18-30	1	4	39	329	40	333
31-50	3	12	26	242	29	254
51-64	0	0	7	21	7	21
65-74	2	20	9	69	11	89
>=75	0	0	1	3	1	3
Total	6	36	82	664	88	700
Phase 2/3 Studies						
18-30	6	41	33	248	39	289
31-50	27	228	56	408	83	636
51-64	31	271	62	548	93	819
65-74	24	224	39	328	63	552
>=75	17	151	26	230	43	381
Total	105	915	216	1762	321	2677

Phase 1 pool includes studies C3601006, C3601007 and D4910C00001 (C3601005).
Phase 2/3 pool includes studies C3601002, C3601009 and D4910C00009 (C3601001).
*MTZ therapy administered to participants with cIAI only.
Person-Time (days) represents the cumulative number of days of exposure of the participants represented in the adjacent Persons column.
[redacted] Source Data: adex Table Generation: 28JUN2023 (15:08)
Output File: ./ATM_AVI_Submissions/ATM_AVI_EMA_RMP/adex_exp_agegrp_sex

Table 12. Duration of Exposure to ATM-AVI by Race, by Ethnicity and by Study Phase - Safety Analysis Set

	ATM-AVI (+/-MTZ)* (N=409)	
	Persons	**Person Time (Days)**
Phase 1 Studies		
Race		
White	56	486
Black or African American	12	105
Asian	18	87
Other*	2	22
Total	88	700
Ethnicity		
African or African-Caribbean	9	88
Asian (Other than Chinese)	6	39
Hispanic or Latino	3	12
Not Hispanic or Latino	23	81
Other**	47	480
Total	88	700
Phase 2/3 Studies		
Race		
White	196	1673
Black or African American	1	9
Asian	109	872
Other*	15	123
Total	321	2677
Ethnicity		
African or African-Caribbean	0	0
Asian (Other than Chinese)	0	0
Hispanic or Latino	82	623
Not Hispanic or Latino	228	1973
Other**	11	81
Total	321	2677

Table 12. Duration of Exposure to ATM-AVI by Race, by Ethnicity and by Study Phase - Safety Analysis Set

	ATM-AVI (+/-MTZ)* (N=409)	
	Persons	**Person Time (Days)**

Phase 1 pool includes studies C3601006, C3601007 and D4910C00001 (C3601005).
Phase 2/3 pool includes studies C3601002, C3601009 and D4910C00009 (C3601001).
*MTZ therapy administered to participants with cIAI only.
Person-Time (days) represents the cumulative number of days of exposure of the participants represented in the adjacent Persons column.
* Race=Other consists of American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Mixed, Not reported, Other.
** Ethnicity=Other consists of Not Applicable, Not reported, Other.
[redacted] Source Data: adex Table Generation: 28JUN2023 (15:08)
Output File: ./ATM_AVI_Submissions/ATM_AVI_EMA_RMP/adex_exp_race_ethnic

Table 13. Duration of Exposure to ATM-AVI by Renal Impairment and by Study Phase - Safety Analysis Set

	ATM-AVI (+/-MTZ)* (N=409)	
Renal Impairment Categories	**Persons**	**Person Time (Days)**
Phase 1 Studies		
Severe (CrCl <=30 mL/min)	0	0
Moderate (CrCl >30 to <=50 mL/min)	5	15
Normal and Mild (CrCl >50 to <=150 mL/min)	6	18
Augmented (CrCl >150 mL/min)	0	0
Total	11	33
Phase 2/3 Studies		
Severe (CrCl <=30 mL/min)	12	91
Moderate (CrCl >30 to <=50 mL/min)	29	271
Normal and Mild (CrCl >50 to <=150 mL/min)	231	1873
Augmented (CrCl >150 mL/min)	48	429
Total	320	2664

Phase 1 pool includes study C3601006 only. C3601007 and D4910C00001(C3601005) are Healthy/Non Renal Participants.
Phase 2/3 pool includes studies C3601002, C3601009 and D4910C00009 (C3601001).
*MTZ therapy administered to participants with cIAI only.
Person-Time (days) represents the cumulative number of days of exposure of the participants represented in the adjacent Persons column.
[redacted] Source Data: adex Table Generation: 28JUN2023 (15:08)
Output File: ./ATM_AVI_Submissions/ATM_AVI_EMA_RMP/adex_exp_renal

Table 14. Duration of Exposure to ATM-AVI by Cardiovascular Impairment, Hepatic Impairment and by Study Phase - Safety Analysis Set

	ATM-AVI (+/-MTZ)* (N=409)	
	Persons	**Person Time (Days)**
Phase 1 Studies		
Cardiovascular Impairment		
Yes	2	6
No	86	694
Total	88	700
Hepatic Impairment		
Yes	0	0
No	88	700
Total	88	700
Phase 2/3 Studies		
Cardiovascular Impairment		
Yes	48	449
No	273	2228
Total	321	2677
Hepatic Impairment		
Yes	26	189
No	295	2488
Total	321	2677

Phase 1 pool includes studies C3601006, C3601007 and D4910C00001 (C3601005).
Phase 2/3 pool includes studies C3601002, C3601009 and D4910C00009 (C3601001).
*MTZ therapy administered to participants with cIAI only.
Person-Time (days) represents the cumulative number of days of exposure of the participants represented in the adjacent Persons column.
Criteria for medical history terms related to hepatic and cardiac impairment are provided in Annex 7.
[redacted] Source Data: adex Table Generation: 28JUN2023 (15:08)
Output File: ./ATM_AVI_Submissions/ATM_AVI_EMA_RMP/adex_exp_hepa_card

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Use in Pregnancy and breastfeeding

Reason for exclusion: ATM-AVI was not studied in pregnant or nursing women.

Is it considered to be included as missing information? No

Rationale: Available information from animal studies do not suggest an increased risk of adverse pregnancy outcome, including foetal malformations. As noted in the SmPC, aztreonam is excreted in human milk in concentrations that are less than 1% of those in simultaneously obtained maternal serum. It is unknown whether avibactam is excreted in human milk. The criterion is not considered as missing information and routine pharmacovigilance can further characterise the safety profile in this population.

Subject has an estimated CrCL ≤15 mL/min by Cockcroft-Gault formula or is receiving hemodialysis or peritoneal dialysis

Reason for exclusion: Subjects on dialysis and/or with renal failure (CrCL ≤15 mL/min) were excluded from the studies.

Is it considered to be included as missing information? No

Rationale: in patients with renal insufficiency, it is recommended that doses of aztreonam are reduced and that there is close monitoring of CrCL. When the dose is appropriately reduced as noted in the SmPC, there is no suggestion that the safety profile of ATM-AVI is different in this population and routine pharmacovigilance is sufficient to monitor this population. It is recommended that patients with CrCL ≤15 mL/min should not receive ATM-AVI unless haemodialysis or another form of renal replacement therapy is instituted. Patients receiving CRRT have not been studied.

Patients with hepatic impairment

Reason for exclusion: Participants were excluded from the Phase 2/3 trials if they had acute hepatitis or acute hepatic failure, cirrhosis or chronic hepatic failure, and if they had elevated liver enzymes (>5x ULN) at Screening which were considered to be not directly related to the infection being treated and/or were not acute in nature.

Is it considered to be included as missing information? No

Rationale: Aztreonam has been associated with transient increases in transaminases. Participants with severe hepatic conditions were excluded from the studies because such participants are likely to have factors which may have confounded safety assessments. Neither avibactam not aztreonam undergo significant hepatic metabolism and therefore systemic clearance of either substance is not expected to be be significantly altered by hepatic impairment.

Pediatric Patients

Reason for exclusion: ATM-AVI was not studied in paediatric patients and this population is not covered by the indications.

Is it considered to be included as missing information? No

Rationale: There is no suggestion that the safety profile of ATM-AVI is different in the paediatric population, compared with non-paediatric population, and there is not an expectation that existing or future pharmacovigilance activities will further characterise the safety and efficacy profile in this population, the criterion is not considered as missing information. A planned Paediatric Investigation Plan (PIP) will evaluate safety in the paediatric population.

Hypersensitivity

Reason for exclusion: ATM-AVI is contraindicated in patients with known hypersensitivity to active substances or to any of the excipients.

Is it considered to be included as missing information? No

Rationale: Hypersensitivity will remain as a contraindication and not as missing information because the data is already available to define this as an important exclusion and no further characterisation therefore is planned.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme may be unlikely to detect certain types of adverse reactions such as rare and very rare adverse reactions or those caused by prolonged exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

There has been limited/no exposure to ATM-AVI in some special populations such as pregnant/lactating women, paediatric participants (<18 years of age), and specific subpopulations that were excluded from the ATM-AVI clinical development program.

Table 15. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program In addition, there are no adequate and well-controlled studies of aztreonam or avibactam in pregnant women.
Breastfeeding women	Not included in the clinical development program.
Paediatric population	Paediatric subjects are not relevant for the proposed indication. Safety in paediatric population will be assessed as part of a Paediatric Investigation Plan.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with some degree of hepatic impairment were treated in the ATM-AVI clinical program (see Module SIV.1 above). No significant differences in the overall safety profile have been found between subjects with and without hepatic impairment. Exposure is available in Module SIII Table 14.
Patients with renal impairment CrCL ≤15 mL/min by Cockcroft-Gault formula or receiving hemodialysis or peritoneal dialysis	Aztreonam and avibactam are predominantly eliminated via the kidneys, therefore the dose of Emblaveo® should be reduced according to the degree of renal impairment There is insufficient data to make dosing adjustment recommendations for patients undergoing renal replacement therapy other than haemodialysis (e.g., continuous veno-venous hemofiltration, or peritoneal dialysis). Exposure of different degrees of renal impairment is available in Module SIII Table 13.
Population with relevant different ethnic origin	For available exposure of subjects with relevant different ethnic origin refer to Module SIII Table 12. There were few data regarding use of ATM-AVI in the Black/African American population.

Module SV. Post-Authorisation Experience

Not applicable as ATM-AVI is not currently marketed.

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

ATM-AVI does not have characteristics that would make it attractive for use for illegal purposes.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Both ATM and the marketed combination product CAZ-AVI are have well-established safety profiles. The safety profile for ATM-AVI can be drawn from available data for ATM and for CAZ-AVI as well as ATM-AVI itself.

Based on the ATM-AVI safety profile and data currently available from the completed Phase 1 and Phase 2a studies and Phase 3 studies, no important identified or potential risks and no missing information for ATM-AVI are proposed to be included in the initial RMP as safety concerns.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not all potential or identified risks for ATM-AVI are considered to meet the level of importance necessitating inclusion in the list of safety concerns in the RMP.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:

- Hepatotoxicity
- *Clostridium difficile* associated diarrhoea

Known risks that require no further characterisation and are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised):

- Hypersensitivity

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

There are no risks considered important for inclusion in the List of Safety Concerns in the RMP.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

There are no important identified risks, important potential risks, and missing information for ATM-AVI.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Not applicable.

Module SVIII. Summary of the Safety Concerns

Table 16. Summary of Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

There are no routine pharmacovigilance activities beyond ADRs reporting and signal detection.

Specific adverse reaction follow-up questionnaires:

None proposed.

Other forms of routine pharmacovigilance activities:

Specific review of AEs (Targeted Medical Events) consistent with Adverse Events of Special Interest. These are AEs pertaining to 3 topics of special interest for the programme: hypersensitivity/anaphylaxis, liver disorders, and *Clostridioides* difficile-associated diarrhoea.

III.2. Additional Pharmacovigilance Activities

No additional pharmacovigilance activities are being proposed.

III.3. Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no plans for post-authorisation efficacy studies.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3. Summary of Risk Minimisation Measures

No safety concerns have been identified and accordingly no additional pharmacovigilance activities and additional risk minimisation activities are necessary.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for EMBLAVEO® (Aztreonam-Avibactam)

This is a summary of the risk management plan (RMP) for EMBLAVEO®. The RMP details important risks of EMBLAVEO®, how these risks can be minimised, and how more information will be obtained about EMBLAVEO®'s risks and uncertainties (missing information).

EMBLAVEO®'s summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how EMBLAVEO® should be used.

This summary of the RMP for EMBLAVEO® should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of EMBLAVEO®'s RMP.

I. The Medicine and What It Is Used For

EMBLAVEO® is indicated for the treatment of the following infections in adult patients:

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

EMBLAVEO® is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.

Further information about the evaluation of EMBLAVEO®’s benefits can be found in aztreonam-avibactam’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of EMBLAVEO® together with measures to minimise such risks and the proposed studies for learning more about EMBLAVEO®’s risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;

Important advice on the medicine's packaging;

The authorised pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of EMBLAVEO® are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EMBLAVEO®. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Table 17. List of important risks and missing information

Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of Important Risk

Not applicable.

II.C Post-Authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for aztreonam-avibactam.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.