CEFTAZIDIME-AVIBACTAM (CAZ-AVI) EUROPEAN UNION RISK MANAGEMENT PLAN

RMP Version number: 4.0

Data lock point for this RMP: 24 February 2025

Date of final sign off: 24 October 2025

Rationale for submitting an updated RMP: Up-version of previous EU-RMP version 3.4 for procedure EMA/VR/0000287802.

1. The MAH is proposing to reclassify the Important Potential Risk of Bacterial resistance development as potential risk, not considered important. The MAH is also proposing to no longer consider the following topics as Missing information: "Pregnancy exposure", "Lactation exposure" and "Immunocompromised population exposure".

Summary of significant changes in this RMP compared to currently approved version 3.3:

RMP Part/Module	**Major Change(s)**
PART I. PRODUCT OVERVIEW	Updated to align the text to the latest version of the SmPC.
PART II. SAFETY SPECIFICATION	
Module SI. Epidemiology of the Indications and Target Populations	Updated to align the indications to the latest version of the SmPC.
Module SII. Non-Clinical Part of the Safety Specification	Updated to propose the removal of the Important Potential Risk of "Bacterial resistance development" and the Missing Information "Pregnancy exposure" and "Lactation exposure".
Module SIII. Clinical Trial Exposure	Minor updates to the body text to remove typos.
Module SIV. Populations Not Studied in Clinical Trials	Updated to propose the removal of the Missing Information "Pregnancy exposure", "Lactation exposure" and "Immunocompromised patient exposure".
Module SV. Post-Authorisation Experience	Updated post-authorization exposure through DLP 24 February 2025.
Module SVI. Additional EU Requirements for the Safety Specification	No changes.
Module SVII. Identified and Potential Risks	Justification provided for the proposal of the removal of: ✓ Important Potential Risk "Bacterial resistance development", and ✓ Missing Information "Pregnancy exposure", "Lactation exposure", and "Immunocompromised population exposure". Cumulative safety database experience for Important Potential Risk of "Hepatotoxicity" updated through 24 February 2025.

RMP Part/Module	Major Change(s)
Module SVIII. Summary of the Safety Concerns	Removal of: ✓ Important Potential Risk "Bacterial resistance development", and ✓ Missing Information "Pregnancy exposure", "Lactation exposure", and "Immunocompromised population exposure".
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORIZATION SAFETY STUDIES)	• Routine PV activities: ✓ Removal of targeted follow-up questionnaire for post-marketing reports related to the Important Potential Risk of "Bacterial resistance development". • Additional PV activities: ✓ Removal of the bacterial resistance development program commitment, which has been fulfilled after providing annual reports for 5 years since the initial MAA in the EU.
PART IV. PLANS FOR POST AUTHORIZATION EFFICACY STUDIES	There are no plans for post-authorisation efficacy studies.
PART V. RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)	Updated according to the changes made to the safety concerns in Module SVII.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Updated according to the changes made to the safety concerns in Module SVII.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	The following annexes have been revised: ✓ Annex 3: Removal of link to protocol for Resistance Surveillance Programme. ✓ Annex 4: Removal of the FU questionnaire for Bacterial resistance development. Revised (simplified) FU questionnaire for Hepatic Events was included. ✓ Annex 7: Updated list of PTs according to MedDRA version 27.1. Removal of Important Potential Risk of "Bacterial resistance development". ✓ Annex 8: Updated summary of changes.

Other RMP versions under evaluation[1]:

RMP Version number: not applicable

Submitted on: not applicable

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Details of the currently approved RMP:

Version number: 3.3

Approved with procedure: EMEA/H/C/004027/II/0035

Date of approval: 21 October 2024

QPPV name [2]: Barbara De Bernardi

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

[1] available on EMA website http://www.ema.europa.eu

[2] 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-authorization application; available on EMA website http://www.ema.europa.eu

LIST OF ABBREVIATIONS

ACH	acute care hospitals
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AmpC	ambler class c enzymes serine-based β-lactamase
APACHE	acute physiology and chronic health evaluation
ASIR	age standardised incidence rates
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
AVI	avibactam
AZ	AstraZeneca
BAL	bronchoalveolar lavage
BAT	best available therapy
BBD	bladder and bowel dysfunction
BLI	β-lactamase inhibitor
BSI	blood stream infection
CA-cUTI	catheter-associated complicated urinary tract infection
CA-UTI	catheter-associated urinary tract infection
CAZ	ceftazidime
CAZ-AVI	ceftazidime-avibactam
CCI	Charlson comorbidity index
CD	Clavien-Dindo
CDAD	*Clostridium difficile*-associated diarrhoea
CE	clinically evaluable
CI	confidence interval
cIAI	complicated intra-abdominal infection
CIAOW	complicated intra-abdominal infections worldwide observational study
cMITT	clinically modified intent-to-treat
CNA	carbapenem non-susceptible *Acinetobacter spp*
COVID-19	coronavirus disease 2019
CPE	carbapenemase-producing Enterobacteriaceae
CrCl	creatinine clearance
CRE	carbapenemase-resistant Enterobacteriaceae
CRKP	carbapenem-resistant *Klebsiella pneumoniae*
CRO	carbapenem-resistant organism
CSP	clinical study protocol
CSR	clinical study report
CT	clinical trial
CTX-M	cefotaximases-m type β-lactamase
cUTI	complicated urinary tract infection
DLP	data lock point
EARS-Net	European Antimicrobial Resistance Surveillance Network

ECDC	European Centre for Disease Prevention and Control
ECF	enterocutaneous fistula
ECG	electrocardiogram/electrocardiographic
EEA	European Economic Area
ELF	epithelial lining fluid
EMA	European Medicines Agency
EOT	end of treatment
EPAR	European public assessment report
ESBL	extended-spectrum ß-lactamases
ESBL-E	extended spectrum β-lactamase-producing Enterobacteriaceae
ESBL-EC	extended spectrum β-lactamase-producing *Escherichia coli*
ESRD	end-stage renal disease
EU	European Union
EU-RMP	European Union risk management plan
EUSCAPE	European Survey on carbapenemase-producing Enterobacteriaceae
FDA	(US) Food and Drug Administration
FU	follow-up
GA	gestational age
GAP	global access programme
GI	gastrointestinal
GN	Gram-negative
GNB	Gram-negative bacteria
GVP	good pharmacovigilance practices
HA	Health Authority
HAI	healthcare-associated infection
HAP	hospital acquired pneumonia
HIC	high-income countries
HMA	Heads of Medicines Agencies
IAI	intra-abdominal infection
ICU	intensive care unit
IDSA	Infectious Diseases Society of America
INICC	International Nosocomial Infection Control Consortium
INN	international non-proprietary name
IQR	inter-quartile range
IRR	incidence rate ratio
IV	intravenous/intravenously
KID	Kids' Inpatient Database
KPC	*Klebsiella pneumoniae* carbapenemase
LB	live births
LFU	late follow-up
LLMIC	low and low and middle-income countries
LMIC	low- and middle-income countries
LTCF	long term care facilities
LTO	limited treatment options
MAA	marketing authorisation application

MAH	marketing authorisation holder
MDR	multidrug-resistant
MDR-GN	multi-drug resistant Gram-negative
MDRO	multidrug-resistant organism
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MeSH	Medical Subject Headings
MITT	modified-intent-to-treat
mMITT	microbiologically modified intent-to-treat
MRGN	multidrug-resistant Gram-negative
MRSA	methicillin-resistant Staphylococcus aureus
MTZ	metronidazole
N/A	not applicable; not available
NDM	New Delhi metallo-β-lactamase
NEC	necrotizing enterocolitis
NICHD	National Institute of Child Health and Human Development
NIS	Nationwide Inpatient Sample
NP	nosocomial pneumonia
NPR	national patient registry
NR	not recommended
NS	neonatal sepsis
OAI	osteoarticular infection
OR	odds ratio
PI	product information
PICU	paediatric intensive care unit
PIP	paediatric investigation plan
PK	pharmacokinetic
PLA	pyogenic liver abscess
PM	post marketing
PMA	postmenstrual age
PND	post natal day
POSAW	prospective observational study on acute appendicitis worldwide
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	periodic safety update report
PT	(MedDRA) Preferred Term
PV	pharmacovigilance
QTc	corrected QT interval
RMM	risk minimisation measure
RMP	risk management plan
ROW	rest of world
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDI	socio demographic index

SMART	study for monitoring antimicrobial resistance trends
SmPC	summary of product characteristics
SMQ	Standardised MedDRA Query
SSI	surgical site infection
TME	targeted medical events
TOC	test of cure
UK	United Kingdom
ULN	upper limit of normal
US	United States
USA	United States of America
UTI	urinary tract infection
VAE	ventilator-associated event
VAP	ventilator-associated pneumonia
VIM	Verona integron-encoded metallo-β-lactamase
VLBW	very low birth weight
VRSA	vancomycin resistant *Staphylococcus aureus*
VUR	vesicoureteral reflux
WHO	World Health Organization

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Ceftazidime and Avibactam (CAZ-AVI)
Pharmacotherapeutic group(s) (ATC Code)	J01DD52 Ceftazidime, combinations
Marketing Authorisation Holder	Pfizer Limited
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Zavicefta
Marketing authorisation procedure	Centralised
Brief description of the product:	Chemical class Ceftazidime-avibactam (also referred to hereafter as CAZ-AVI) comprises ceftazidime, an established injectable third-generation cephalosporin antimicrobial agent (FORTUM), and avibactam (formerly NXL104, AVE1330), a novel non-β-lactam β-lactamase inhibitor with a spectrum including Ambler Class A extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemase (KPC) Class A enzymes, Class C (AmpC) enzymes, and some Class D (OXA-48) enzymes.
	Summary of mode of action Ceftazidime inhibits bacterial peptidoglycan cell wall synthesis following binding to penicillin-binding proteins, which leads to bacterial cell lysis and death. Ceftazidime is active against many important Gram-negative and Gram-positive bacterial pathogens in vitro, especially *Enterobacteriaceae* and *Pseudomonas aeruginosa*. Avibactam has no effective intrinsic antimicrobial activity. Inhibition of β-lactamases by avibactam occurs by the formation of a highly stable covalent bond with the enzyme. The addition of avibactam to ceftazidime expands its antibacterial activity against pathogens possessing β-lactamases that are susceptible to inhibition by avibactam; it therefore has the potential to restore the utility of ceftazidime in the clinical setting.
	Important information about its composition AVI does not inhibit Class B enzymes (metallo-β-lactamases) and is not able to inhibit many of the Class D enzymes.
Hyperlink to the Product Information:	Please refer to Module 1.3.1 of this submission.
Indication(s) in the EEA	**Current:** Zavicefta is indicated in adults and paediatric patients from birth for the treatment of the following infections: • Complicated intra-abdominal infection (cIAI). • Complicated urinary tract infection (cUTI), including pyelonephritis. • Hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP).

	Treatment of adult patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above. Zavicefta is also indicated for the treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients from birth with limited treatment options. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Dosage in the EEA	**Current:** Recommended intravenous dose for adults with estimated CrCL > 50 mL/min. **Table 1. Recommended intravenous dose for adult patients with estimated CrCL ≥ 50 mL/min[a]** **Type of infection** / **Dose of (CAZ-AVI)** / **Frequency** / **Infusion time** / **Duration of treatment** cIAI[b,c] / 2 g/0.5 g / Every 8 hours / 2 hours / 5-14 days cUTI, including pyelonephritis[c] / 2 g/0.5 g / Every 8 hours / 2 hours / 5-10 days[d] HAP/VAP[c] / 2 g/0.5 g / Every 8 hours / 2 hours / 7-14 days Bacteraemia associated with, or suspected to be associated with any of the above infections / 2 g/0.5 g / Every 8 hours / 2 hours / Duration of treatment should be in accordance with the site of infection. Infections due to aerobic Gram-negative organisms in adults patients with limited treatment options[b,c] / 2 g/0.5 g / Every 8 hours / 2 hours / Guided by the severity of the infection, the pathogen(s), and the patient's clinical and bacteriological progress[e] a. CrCl estimated using the Cockcroft-Gault formula. b. To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process. c. 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. d. The total duration shown may include intravenous Zavicefta followed by appropriate oral therapy. e. There is very limited experience with the use of Zavicefta for more than 14 days. *Dosage in paediatric patients with creatinine clearance (CrCL) >50 mL/min/1.73 m^2)* **Table 2. Dosage in paediatric patients from 3 months of age with estimated CrCL[a] ≥ 50 mL/min/1.73 m^2** **Type of infection** / **Age group[h]** / **Dose of ceftazidime/ avibactam[g]** / **Frequency** / **Infusion time** / **Duration of treatment** cIAI[b,c] OR cUTI including pyelonephritis[c] OR HAP/VAP[c] / 6 months to <18 years / 50 mg/kg/ 12.5 mg/kg **to a maximum of** 2 g/0.5 g / Every 8 hours / 2 hours / cIAI: 5-14 days cUTI[d]: 5-14 days HAP/VAP 7-14 days LTO: Guided by the severity of the 3 months to < 6 months[f] / 40 mg/kg / 10 mg/kg / Every 8 hours / 2 hours

OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO)[b,c]						infection, the pathogen(s) and the patient's clinical and bacteriological progress[e]

a. CrCL estimated using the Schwartz bedside formula.
b. To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
c. 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.
d. The total treatment duration shown may include intravenous Zavicefta followed by appropriate oral therapy.
e. There is very limited experience with the use of Zavicefta for more than 14 days.
f. There is limited experience with the use of Zavicefta in paediatric patients 3 months to <6 months (see section 5.2.)
g. Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).
h. Paediatric patients studied from 3 to 12 months of age were full term (≥ 37 weeks gestation).

Table 3. Dosage in paediatric patients less than 3 months of age[a]

Type of infection	Age group		Dose of ceftazidime/ avibactam[b]	Frequency	Infusion time	Duration of treatment
cIAI[c,d] OR cUTI including pyelonephritis[d] OR HAP/VAP OR Infections due to aerobic Gram-negative organisms in patients with limited treatment options (LTO) [c,d]	Full term neonates and infants	> 28 days to < 3 months	**30 mg/kg**/7.5 mg/kg	Every 8 hours	2 hours	cIAI: 5-14 days cUTI[f]: 5-14 days HAP/VAP 7-14 days LTO: Guided by the severity of the infection, the pathogen(s) and the patient's clinical and bacteriological progress[e]
		Birth to ≤ 28 days	**20 mg/kg**/5 mg/kg			
	Preterm neonates and infants[h]	> 44 weeks to < 53 weeks PMA[g]	**30 mg/kg**/7.5 mg/kg	Every 8 hours	2 hours	
		31 to ≤ 44 weeks PMA[g]	**20 mg/kg**/5 mg/kg			
		26 to < 31 weeks PMA[g,i]	**20 mg/kg**/5 mg/kg	Every 12 hours	2 hours	

a. Patients with serum creatinine at or below the upper limit of normal for age.
b. Ceftazidime/avibactam is a combination product in a fixed 4:1 ratio and dosage recommendations are based on the ceftazidime component only (see section 6.6).
c. To be used in combination with metronidazole when anaerobic pathogens are known or suspected to be contributing to the infectious process.
d. 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.
e. There is very limited experience with the use of Zavicefta for more than 14 days.

	f. The total treatment duration shown may include intravenous Zavicefta followed by appropriate oral therapy. g. Postmenstrual age. h. Preterm defined as < 37 weeks gestation. i. Dose recommendations for patients 26 to < 31 weeks PMA are based on pharmacokinetic modelling only (see section 5.2). Special populations *Elderly population:* see SmPC section 4.2. *Renal impairment:* see SmPC section 4.2. *Dosage in adults and paediatric patients (3 months and older) with CrCL <50 mL/min/1.73 m^2:* see SmPC section 4.2 *Hepatic impairment:* see SmPC section 4.2.
	Method of administration Intravenous use. Zavicefta is administered by intravenous infusion over 120 minutes in an appropriate infusion volume (see section 6.6). For instructions on reconstitution and dilution of the medicinal product before administration see section 6.6.
Pharmaceutical form(s) and strengths	**Current:** Powder for concentrate for solution for infusion (powder for concentrate). A white to yellow powder. Each vial contains CAZ pentahydrate equivalent to 2 g CAZ and AVI sodium equivalent to 0.5 g AVI. After reconstitution, 1 mL of solution contains 167.3 mg of CAZ and 41.8 mg of AVI.
Is/will the product be subject to additional monitoring in the EU?	No

AVI = Avibactam; CAZ = Ceftazidime; CrCl = Creatinine Clearance; EEA = European Economic Area; EU = European Union; IV = Intravenous.

PART II. SAFETY SPECIFICATION

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

Indication:

Ceftazidime-avibactam (CAZ-AVI) is indicated for the treatment of the following infections in in adults and paediatric patients from birth:

- Complicated Intra-Abdominal Infection (cIAI).
- Complicated Urinary Tract Infection (cUTI), including pyelonephritis.
- Hospital-Acquired Pneumonia (HAP), including Ventilator-Associated Pneumonia (VAP).
- Treatment of infections due to aerobic Gram-negative organisms in adults and paediatric patients from birth with limited treatment options.

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

SI.1. Indication: Complicated Intra-Abdominal Infections

Complicated intra-abdominal infections may be caused by a large variety of disease entities and require both surgical or radiological drainage and antimicrobial therapy.[1] In general, cIAI is represented by intra-abdominal abscesses or peritonitis, occurring due to the entry of enteric microorganisms into the peritoneal cavity through a defect in any abdominal viscus or the intestinal wall, as a result of obstruction, infarction or direct trauma.[1]

A search of the literature was conducted using MEDLINE via PubMed to identify non-interventional studies conducted among the adult population diagnosed with cIAI published from January 2019 to August 2023. Search terms included (incidence, prevalence, epidemiology, mortality, morbidity, comorbidity or risk factors) and (complicated intra-abdominal infections). The search also included common sources of cIAI such as acute appendicitis with peritoneal abscess, acute appendicitis with generalized peritonitis, appendiceal perforation, peri-appendiceal abscess, secondary peritonitis, gastroduodenal perforations, or small bowel perforations.

A similar approach of literature search for paediatric and neonatal population was applied. For neonates, considering paucity of the epidemiology studies, literature search was expanded to the last 10 years (beginning January 2014) and included common sources of cIAI in neonates such as neonatal appendicitis and necrotizing enterocolitis (NEC), a precursor condition leading to cIAI.[2]

SI.1.1. Indication: Complicated Intra-Abdominal Infections (Adult Population)

Incidence:

Intra-Abdominal Infections (IAIs) are common in clinical practice and comprise a wide variety of clinical presentations and differing sources of infection.[3, 4] The infections can involve the entire peritoneal cavity or retroperitoneal spaces or can be localised with one or more abscesses surrounding diseased or perforated viscera. Wide varieties of bacterial pathogens are responsible for cIAI, including Gram-negative aerobic bacteria, Gram-positive bacteria, and anaerobic bacteria; mixed infections also occur.

However, Gram-negative organisms such as *Escherichia coli* and *Klebsiella* species are commonly associated with IAIs.[5] In general, compared with uncomplicated IAI, cIAI extend beyond local viscera into peritoneal or retroperitoneal spaces and are associated with systemic signs and symptoms of illness.

The overall incidence of cIAI is difficult to establish and varies with the underlying abdominal disease process. As such, the incidence of common, underlying intra-abdominal diseases is described in this section.

The global age-standardized, annual incidence rate of appendicitis was 229.9 cases per 100,000 persons, as reported by the Global Burden of Disease study conducted between 1990 to 2019 on 672,203 appendicitis cases from 204 countries.[6] The pooled annual incidence of appendicitis or appendectomy ranged from 105 to 151 cases per 100,000 person-years in Europe, and 100 cases per 100,000 person-years in North America in the 21st century, as reported by a systematic review on 120 population-based studies.[7] The reported incidence for pyogenic liver abscess (PLA) (5.2 cases per 100,000 person-years) and sigmoid diverticulitis (41.3 cases per 100,000 persons) in observational studies from Sweden[8] and Finland[9], respectively.

In the US, the reported incidence for acute appendicitis was 106 cases per 100,000 person-years.[10] The incidence of perforated appendicitis was 29 cases per 100,000 person-years.[10]

Prevalence:

The overall prevalence of cIAI in Europe was not identified from the literature.

Globally, the age-standardized prevalence rate of appendicitis was 8.7 cases per 100,000 persons (95% CI: 6.9 - 11.0) in 2019. In various regions of Europe, it ranged between 8.4 to 10.6 cases per 100,000 individuals. However, it differed from region to region in America with the highest rate in Andean Latin America (32.5 cases per 100,000 individuals) followed by central Latin America (13.6 cases per 100,000 individuals) and high-income North America (6.2 cases per 100,000 individuals). Data in South Asia showed similar prevalence of appendicitis as Europe (10 cases per 100,000 individuals) in the Global Burden of Disease Study.[6]

In pregnant patients, a nationwide inpatient sample (NIS) study identified a prevalence rate of 10.7 acute appendicitis cases per 10,000 hospitalizations (63,145 of 58 million pregnancy hospitalizations from 1 January 2002, through 31 December 2015) in the US.[11]

Regarding the relative proportion of individual cIAI, out of 1,898 patients who were followed and treated for cIAI in the Complicated Intra-Abdominal Infections Worldwide Observational Study (CIAOW study), from October 2012 to March 2013, 86.7% (1,645 of 1,898) of patients were affected by community-acquired infections, and 13.3% (253 of 1,898) suffered from healthcare-associated infections (HAIs).

Generalised peritonitis was experienced by 43.6% (827 of 1,898) of patients, and 56.4% (1,071 of 1,898) of patients suffered from localised peritonitis or abscesses.[12]

The proportion of primary peritonitis from an international, multicentre, prospective, observational cohort study from January to December in 2016 was 3.9% (103 primary peritonitis cases of 2,621 ICU admissions with intra-abdominal infections).[13] This appeared lower compared to the prevalence of complicated diverticulitis (33% [187 complicated diverticulitis cases of 561 colonic diverticulitis]), as reported by a patient-records-based retrospective study in Germany from February 2009 to December 2017.[14]

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

Age, gender, and race/ethnicity

In the CIAOW study, the mean age was 51.6 years (range 18-99 years); 41% were women and 59% were men.[12] In the Prospective Observational Study on acute Appendicitis Worldwide (POSAW) study that included 4,282 acute appendicitis patients, the median age was 29 years (IQR: 21-44 years).[15]

The mean age reported based on five observational studies conducted in the European Union among patients with cIAI was 63.1 ± 14.0 years.[16] Country-specific studies from the United Kingdom (UK) and European region reported the age ranging from 30-38 years for acute appendicitis[17, 18] and 71 years for PLA (Table 4).[16]

Compared to the European studies, the US studies reported age of patients with appendicitis ranging from 15 to 49 years.[10, 11]

None of the retrieved European studies reported racial distribution. A study on 64,408 American pregnant women with appendicitis reported highest proportion of non-Hispanic white (Table 4).[11]

Demographic details for patients with cIAI and subtypes (e.g., acute appendicitis, PLA) are described in Table 4.

Table 4. Demographics of individual intra-abdominal infections in adult population

Sr#	Author Year	Sample size	Design	Age (mean ±SD) or (median (IQR))	Gender (Male)	Race	Region
1	York TJ 2020[18]	703 acute appendicitis patients	Longitudinal study from September 2012 to August 2019	38 years	52.1% (366 of 703)	Not available	UK
2	Sisik A 2021[17]	3,296 acute appendicitis patients	Retrospective study from January 2007 to December 2016	30.42±12 years	67.7% (2,331 of 3,296)	Not available	Turkey
3	Svensson E 2023[8]	364 pyogenic liver abscess patients	Observational study from 2011 to 2020	71 years (IQR: 3-97)	57% (206 of 364)	Not available	Sweden
4	Golz RA 2020[10]	35,730 acute appendicitis patients	Retrospective study from 2008 to 2012	29 years (IQR: 16-48)	53.6% (19,156 of 35,730)	Not available	US
5	Dongarwar D 2020[11]	64,408 pregnant appendicitis patients	Retrospective cross-sectional study NIS from January 2002 to December 2015	15-24 years: 40.7% (19,785,950 patients of 58,784,013) 25-34 years: 47.4% (30,366,510 patients of 58,784,013) 35-49 years: 11.9% (8,631,553 patients of 58,784,013)	N/A	Non-Hispanic white: 46.1% (24,995,486 of 58,784,013) Hispanic: 19.5% (10,801,987 of 58,784,013) non-Hispanic black: 8.5% (7,141,952 of 58,784,013)	US

IQR=Inter Quartile Range; NIS=National Inpatient Sample; SD=Standard Deviation; UK=United Kingdom; US=United States

Risk factors

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, HAIs, 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, organ failure, gastrointestinal (GI) obstruction, and chronic pelvic fistulizing disease.[3, 12, 19-21] A study by Liu et al., also identified carbapenem-resistant *Enterobacteriaceae* infection as a risk factor for cIAI related mortality.[22]

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 (i.e.., 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.

The choice of antibiotics depends on the likelihood of resistant pathogens being present at the local institution. In general, the chance of resistant pathogens is higher for hospital-acquired cIAI and in patients who have received antibiotics recently.

The Infectious Diseases Society of America (IDSA) provides recommendations for antimicrobial therapy for healthcare-associated cIAI.

Table 5. Treatment recommendations - Intra-abdominal infections based on causative microorganism

Organism seen at healthcare institution	Regimen				
	Imipenem cilastatin, meropenem, or doripenem	Piperacillin-tazobactam	Ceftazidime or cefepime, each with metronidazole	Aminoglycoside	Vancomycin
<20% Resistant *P. aeruginosa*, β (ESBL)-producing *Enterobacteriaceae, Acinetobacter*, or other multidrug-resistant Gram-negative bacilli	R	R	R	NR	NR
ESBL-producing *Enterobacteriaceae*	R	R	NR	R	NR
P. aeruginosa >20% resistant to ceftazidime	R	R	NR	R	NR
Methicillin-resistant Staphylococcus aureus	NR	NR	NR	NR	R

Source: [4]
ESBL = Extended-Spectrum β-Lactamase; R = Recommended; NR = Not Recommended.

The duration of antibiotic treatment of established infection should be limited to 4 to 7 days unless it is difficult to achieve adequate infection source control.[4]

According to the guidance from Stanford Health on empirical antimicrobial treatment for acute appendicitis with community-acquired infection, without sepsis or septic shock using antimicrobials, the ceftriaxone 2 g intravenous (IV) q 24 hours with metronidazole 500 mg orally (PO) q 8 hours was recommended. Whereas, for community-acquired infection with

sepsis or septic shock, piperacillin-tazobactam 4.5 g IV q 8 hours of extended infusion was recommended to be the first-line treatment regimen. The recommended regimen of antimicrobials is worth 10 days, is recommended to be discontinued within 24 hours if appendectomy is required. In case of acute appendicitis with appropriate surgical source control, the antimicrobial therapy can be discontinued after 4 days.

The empirical treatment for complicated diverticulitis with community-acquired infection without sepsis or septic shock included ceftriaxone 2 g intravenous IV q 24 hours with metronidazole 500 mg PO q 8 hours for a duration of 5-7 days. After appropriate source control procedures such as percutaneous drainage or surgery for treating community-acquired infection with sepsis or septic shock, the recommended first-line regimen was piperacillin-tazobactam 4.5 g IV q 8 hours of extended infusion for 4 days.[23]

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

Mortality

Mortality rates varied according to the source of infection: 0.25% and 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%).[24-26]

Mortality rates are summarized in Table 6. Specifically, the 6-month mortality rates in patients with cIAI and acute appendicitis were 10.5% in the CIAOW study and 0.28% in the POSAW study.[12, 15] A multiple-centre observation study in UK among 417 patients with cIAI reported a 72-hour mortality rate post cIAI diagnosis of 11.3%.[27]

Table 6. Mortality of individual intra-abdominal infections in adult population

Sr #	Author Year	Sample size	Design	Mortality rate	Region
1	Sartelli M 2014 (CIAOW Study)[12]	1,898 cIAI patients	Multicenter observational study from October 2012 to March 2013	10.5% (199 of 1,898) (overall during 6-months study period)	Global
2	Sartelli M 2018 (POSAW Study)[15]	4,282 acute appendicitis patients	Prospective observational study from April 2016 to September 2016	0.28% (12 of 4,282) (overall during 6-months study period)	Global
3	Ahmed S 2021[27]	417 cIAI patients	Multicenter observational study from 2016 to 2017	11.3% (47 of 417) (72-hour mortality rate post cIAI diagnosis)	UK
4	Sell NM 2020[21]	44,915,066 diverticulitis patients	Retrospective cohort study from 1999 to 2016.	0.12% (55,096 of 44,915,066) (total mortality rate in the study period from 1999-2016)	US

cIAI = Complicated Intra-abdominal Infections; CIAOW= Complicated Intra-Abdominal Infections Worldwide Observational Study; POSAW = Prospective Observational Study on Acute Appendicitis Worldwide; UK = United Kingdom; US = United States

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.[28, 29] Morbidities associated with negative appendectomies include wound infection, intestinal obstruction, and septicaemia.[30] Untreated or poorly treated IAIs may complicate intra-abdominal abscess and sepsis.[12]

Important co-morbidities:

The important comorbidities associated with cIAI included malignancy,[31, 32] cardiovascular disease,[12, 33] diabetes,[16, 34] hypertension,[34] immunosuppression,[15] respiratory diseases, and renal diseases.[35, 36]

SI.1.2. Indication: Complicated Intra-Abdominal Infections (Paediatric Population)

Incidence:

The common causes reported for cIAI in children include typhoid ileal perforation and appendicitis, followed by cholecystitis, tuberculous peritonitis, and complicated intussusception.[37] On average, one-third of paediatric patients who present with appendicitis have advanced disease or perforation, placing them at increased risk for post-operative complications, such as intra-abdominal abscess formation.[38]

The overall incidence of cIAI among paediatric patients was not identified from the literature. cIAI depend on the clinical diagnosis.[39] Incidence for common sources of cIAI among paediatric patients (i.e., appendicitis, PLA) is summarized in this section.

The incidence of appendicitis rises from 1 to 2 cases per 10,000 children per year between birth and 4 years to 25 cases for every 10,000 children per year between 10 and 17 years.[40] Appendiceal perforation is nearly universal in children 3 years or younger compared with less than 15% in adolescents.[41]

In population-based studies, the incidence proportion of perforated appendicitis in patients who required surgery ranged from 22.5% to 38%.[42-47]

The incidence of perforating appendicitis reported in Denmark (1.56 to 6.05 per 10,000 patients) and Sweden (13.5 per 100,000 person-years) were similar. However, for specific age group such as children 10-14 years, a higher rate was noted in Sweden (> 50 per 100,000 person-years).[48, 49] Another study in Sweden reported incidence of complicated appendicitis of 16.8% (95% CI: 16.7-17.0).[50] The reported incidence for PLA in the US was 13.5 per 100,000 hospitalizations.[51] In UK, a retrospective study reported an annual incidence range of acute appendicitis of 1.13 to 1.66 per 1,000 children.[52] The details about these studies are summarized in Table 7.

Table 7. Incidence of individual intra-abdominal diseases in paediatric population

Sr #	Author Year	Sample size	Design	Incidence proportion /Incidence rate	Region
1	Andersen SB 2009[48]	28,274 acute appendicitis patients	Retrospective study based on the discharge diagnoses taken from National Patient Registry (NPR) and the Statbank Denmark webpage from 1996 to 2004	1.56 to 6.05 cases per 100,000 patients (15.6 to 60.5 per 100,000) (perforating appendicitis)	Denmark
2	Almström M 2018[49]	64,971 children registered for Swedish National Patient Register (NPR)	Population-based cohort study based on Swedish NPR from 1987 to 2013	100.1 cases per 100,000 person-years (acute appendicitis) 19.9 cases per 100,000 person-years (perforating appendicitis)	Sweden
3	Kumar J 2017[52]	475 acute appendicitis patients who underwent emergency appendectomy (Group 1*: N=188 Group 2**: N=287)	Retrospective study from 2007 to 2008	1.13 to 1.66 cases per 1,000 children per year (acute appendicitis)	UK
4	Omling E 2019[50]	38,939 appendicitis patients	Nation-wide cohort study using the longitudinal registry data from 2001 to 2014	16.8% (6,561 of 38,939 appendicitis patients) (complicated appendicitis)	Sweden
5	Thavamani A 2020[51]	4,075 patients with pyogenic liver abscess	Retrospective study of NIS and Kids Inpatient Database (KID) from 2003 to 2014.	13.5 cases per 100,000 hospitalizations (pyogenic liver abscess)	US

*Children who underwent emergency appendectomy between June 2001 and May 2003.
** Children who underwent emergency appendectomy between January 2007 and December 2008
KID = Kids Inpatient Database; NPR = National Patient Registry; UK = United Kingdom; US = United States

Prevalence:

The overall prevalence of cIAI among paediatric patients was not identified from the literature.

The most common cause for surgical emergency amongst children is acute appendicitis (1-2% in paediatrics surgical admissions).[53] For children in emergency department with acute abdominal pain, 1-8% were diagnosed with appendicitis.[54] Due to failure in early diagnosis, most of the children presented with appendicular perforation.[55]

The prevalence of perforated appendicitis among children with appendicitis was approximately 30% (Table 8).[56, 57]

Table 8. Prevalence of perforated appendicitis in paediatric population

Sr #	Author Year	Sample size	Design	Prevalence (Perforated appendicitis)	Region
1	Zvizdic Z 2021[56]	295 appendicitis patients who had undergone appendectomy	Retrospective study of medical records from 2013 to 2015	31.2% (92 cases of 295)	Europe
2	Baxter KJ 2018[57]	19,109 appendicitis patients	Retrospective study of Truven MarketScan national insurance claims database from January 2010 to December 2013	28.8% (5,509 cases of 19,109)	US

US = United States

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

Age, gender, and race/ethnicity

Age appeared to be a risk factor for perforated appendicitis in children (Table 9). Perforated appendicitis and pyogenic liver abscess were also more likely to occur in boys (Table 9). A cohort study in England reported an incidence of 1.99 per 1,000 boys per year compared with 1.32 per 1,000 girls per year between January 2007 and December 2008.[52]

Table 9. Demographics of perforated appendicitis in paediatric population

Sr #	Author Year	Sample size	Design	Incidence proportion (%)/rate (per 10,000) (Perforated appendicitis)	Age group	Region
1	Almström M 2017[46]	2,756 perforated appendicitis patients	Retrospective study from 2006 to 2013	16.2% (107 of 661)	>5 years	Sweden
				32.7% (216 of 661)	5-10 years	
				51.1% (338 of 661)	10-15 years	
2	Andersen SB 2009[48]	28,274 acute appendicitis patients	Retrospective study based on the discharge diagnoses taken from National Patient Registry (NPR) and the Statbank Denmark webpage from 1996 to 2004	Male: 1.95 Female: 1.56	<4 years	Denmark
				Male: 4.47 Female: 4.81	5-9 years	
				Male: 6.05 Female: 5.28	10-14 years	
				Male: 4.67 Female: 3.92	15-19 years	

NPR = National Patient Registry

No major difference was seen in mean or median age between the EU and the US studies. Boy-girl ratio reported in all studies was around 60%-40%.[51, 56, 57] In the US, Caucasians were more likely to have PLA compared to Hispanic and African Americans.[51] The demographic and racial/ethnic characteristics of these studies are presented in Table 10.

Table 10. Demographics of individual intra-abdominal infections in paediatric population

Sr #	Author Year	Sample size	Age (mean ±SD) or (median (IQR))	Gender proportion	Race	Region
1	Zvizdic Z 2021[56]	295 perforated appendicitis patients	10 years (IQR: 8-13)	Male: 58.3% (172 of 295) Female: 41.7% (123 of 295)	Not available	Europe
2	Baxter KJ 2018[57]	19,109 perforated appendicitis patients	12.39 ± 3.88 years	Male: 59.8% (11,422 of 19,109)	Not available	US
3	Thavamani A 2020[51]	4,057 pyogenic liver abscess patients	13.3±6.1 years	Male: 61% (2,474 of 4,057) Female: 39% (1,583 of 4,057)	Caucasian: 42.5% (1,723 of 4,507) Hispanic: 21.1% (857/4,507) African American: 12.3% (500 of 4,507)	US

IQR = Inter Quartile Range; SD = Standard Deviation; US = United States

Risk factors

Among paediatric patients with perforated appendicitis, risk factors at presentation for the formation of intra-abdominal abscess include diarrhoea, age, weight, and body mass index.[38] At the time of surgery, an intra-operative appendicolith is associated with an increased incidence of intra-abdominal abscess development.[38] Post-operative risk factors that have been suggested include lymphocyte depression, fever on post-operative day 3, and an increased white blood cell count on post-operative day 5.[38] In children, cIAI mostly occurs due to acute appendicitis followed by infection of the enteric flora. The most common microorganisms isolated from the intra-abdominal culture were *Bacteroides fragilis* and *Escherichia coli*. It can also be caused by *Pseudomonas aeruginosa*, facultative anaerobes, and Gram-positive cocci.[58]

Risk factors in children less than 2 years old:

In the first 9 to 12 months of life, the caecum is tapered, and the appendix is funnel shaped making it less prone to obstructions and this, combined with a soft-food diet, and less prominent lymphoid tissue are believed to account for the lower incidence of appendicitis in infancy.

Additionally, seasonal variation in the presentation of appendicitis has been observed which may be due, in part, to seasonal outbreaks of enteric infections. Extended breast-feeding appears to significantly diminish the risk of developing appendicitis. It has been postulated that a milk-induced alteration of the immune response makes lymphoid tissue at the base of the appendix less reactive later in life.

Alternately, prolonged breast-feeding may be a surrogate marker for an unknown socioeconomic or dietary feature that diminishes the risk of appendicitis. There is a genetic

predisposition for developing appendicitis. A history of appendicitis in a first-degree relative is associated with a 3.5 to 10.0 relative risk for developing this disorder. The strongest familial associations have been noted when children develop appendicitis at unusually young ages (birth to 6 years).

The main existing treatment options:

For paediatric patients, the IDSA guidelines recommend that antimicrobial therapy be based on a combination of factors including whether the infection was community - or healthcare - acquired, the severity of illness, and the safety of the antimicrobial agents in specific paediatric age groups. Broad-spectrum antimicrobial regimens recommended for initial treatment in paediatric patients with either community - or healthcare-acquired cIAI include aminoglycoside-based regimens, carbapenems (imipenem, meropenem, or ertapenem), β-lactam/β-lactamase-inhibitor combinations, such as piperacillin-tazobactam, or advanced-generation cephalosporins (cefotaxime, ceftriaxone, ceftazidime, or cefepime) given in combination with metronidazole. Additionally, combinations of gentamicin or tobramycin, each given with metronidazole or clindamycin, and with or without ampicillin, may also be considered. For paediatric patients who are unable to receive β-lactam antibiotics due to severe reactions, it is recommended that ciprofloxacin plus metronidazole or an aminoglycoside-based regimen be used.[4] The duration of antibiotic treatment of established infection, as in adults, should be limited to 4 to 7 days, unless it is difficult to achieve adequate infection source control.[4]

For paediatric patients diagnosed with appendicitis, the Children's hospital of Philadelphia suggested several clinical pathways including both non-operative, operative and post operative management. In post-operative management, key clinical scenarios included were acute appendicitis (perforated and non-perforated), post-operative abscess, delayed appendectomy in patients with perforated appendicitis with abscess.

For non-perforated appendicitis, no post-operative antibiotics were recommended. However, for perforated appendicitis, Ceftriaxone/Metronidazole until normal vital signs, tolerating diet, and ambulating condition was recommended.

Perforated appendicitis in paediatric patients was recommended to treat using a combination of ceftriaxone (50 mg/kg/dose IV q24h) or ciprofloxacin (15 mg/kg/dose IV q12h) (in case of severe penicillin or cephalosporine allergy) with metronidazole (30 mg/kg/dose IV q24h), followed by abscess culture and continuation of source control treatment. Piperacillin-tazobactam was recommended in the case of non-drainable abscess besides infectious disease specialist guidance and consultation.[59]

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

<u>Mortality</u>

No data on mortality rates were identified for overall cIAI among paediatric patients. The in-hospital mortality rate of PLA was 0.8% (n=32 deaths out of 4,057 admissions), as reported

by a population-based analysis of NIS and Kids Inpatient database (KID) database from 2003 to 2014 in the US.[51]

Morbidity

Factors consistently associated with poor outcomes in paediatric patients with intra-abdominal infections include increased illness severity, failed source control, inadequate empiric antimicrobial therapy and healthcare-acquired infection.[39] Early prognostic evaluation of cIAI is important to select high-risk patients for more aggressive therapeutic procedures.[39] For cases of appendicitis, a clinical diagnosis is often difficult, and a delayed diagnosis may result in perforation of the inflamed appendix, peritonitis, or intra-abdominal abscess formation.[42] Surgical interventions are also followed by surgical site infections (SSI), dehiscence of wounds, and burst abdomen. The other associated complications include enterocutaneous fistula (ECF), septicaemia, chest infections, and intra-abdominal abscess.[60]

Important co-morbidities

Important comorbid conditions among paediatric patients with cIAI include diagnosis of a gastrointestinal, respiratory or urinary infection,[61] hepatobiliary malignancies, liver transplant, biliary diseases, inflammatory bowel disease, other GI malignancies, and primary immune deficiency disorders.[51]

SI.1.3. Indication: Complicated Intra-Abdominal Infections (Neonatal Population)

The epidemiological data for overall cIAI in neonates were not identified from the retrieved literature.

NEC is a condition characterized by intestinal tissue inflammation and death, primarily affecting premature infants. In the context of cIAI, the inflammatory damage caused by cIAI can create an environment that increases the risk of NEC development, especially in vulnerable populations like premature infants. Hence, it can serve as an indirect indicator for estimating the disease burden. Therefore, epidemiological data on individual intra-abdominal disease (e.g., acute appendicitis) and NEC are reported for this indication.

Incidence:

Neonatal appendicitis is a rare condition with a global incidence of 0.04% to 2%.[62] As it mimics other common abdominal conditions such as NEC, obstruction, and gastroenteritis, its incidence is challenging to estimate.[63]

A systematic literature review and meta-analysis estimated a pooled incidence of NEC in newborns with very low birth weight as 6.0% [95% CI: 4.0- 9.0%].[64] The pooled incidence based on 27 cohort studies from 1993 to 2018 in North America, Western Europe, and Australia is 4.3% (95% CI: 2.5- 6.6%).[64] The incidence of NEC in a multicenter study from January 2005 to December 2017 using Spanish Neonatal Network was 8.8% during whole study period.[65] The incidence rate of NEC was 3.4 cases per 10,000 live births in Sweden from 1987 to 2009.[66]

The incidence of NEC in neonates is summarised in Table 11.

Table 11. Incidence of necrotising enterocolitis in neonatal population

Sr #	Author Year	Sample size	Design	NEC incidence rate	Region
1	Alsaied A 2020[64]	27 cohort studies reporting the incidence of NEC	Systematic review and meta-analysis.	Global pooled incidence: 6.0% [95% CI: 4.0- 9.0%] Pooled incidence in North America, Western Europe, and Australia: 4.3% [95% CI: 2.5- 6.6%]	Global
2	Ahle M 2013[66]	2,381,318 live births	Retrospective cohort study of the National Patient Register from 1987 to 2009	3.4 cases in 10,000 live births	Sweden
3	Zozaya C 2020[65]	25,821 preterm infants <32 weeks of gestational age	Multicenter cohort study and data from the Spanish Neonatal Network from 2005 to 2017.	8.8% cases of 25,821 included infants	Spain

CI = Confidence Interval; NEC = Necrotizing Enterocolitis

Prevalence:

The prevalence of cIAI or individual intra-abdominal diseases in neonatal population was not identified from the retrieved literature.

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

Age, gender, and race/ethnicity

The proportion of male neonates with appendicitis or NEC was higher than female neonates, ranging 51 – 56%.[67] For NEC, the incidence in male newborns was 3.7 cases per 10,000 live births as compared to 3.0 cases per 10,000 live births among female newborns (Table 12).[66]

Table 12. Demographics of individual intra-abdominal infections in neonatal population

Sr #	Author Year	Sample size	Design	Age	Gender proportion	Race	Region
1	Raveenthiran V 2015[67]	50 neonatal appendicitis cases	Case review	Not specified	Males: 56%(29 of 50) Female: 44 % (21 of 50)	Not available	Global
2	Ahle M 2013[66]	2,381,318 live births and 808 NEC patients with available perinatal data	Retrospective cohort study of the National Patient Register from 1987 to 2009	145 full-term babies, 138 between 32-26 weeks, 220 between 28-31 weeks, and 304 less than 28 weeks	Males: 3.7 per 10,000 live births Female: 3.0 per 10,000 live births Male : 51.37% Female: 48.6%	Not available	Sweden

NEC = Necrotizing Enterocolitis

Risk factors

The important risk factors for cIAI in neonates are low birth weight, small for gestational age, poor surgery, cIAI aetiology, and poor antibiotic treatment for enterococci.[34] Several other risk factors included clinical chorioamnionitis, feed intolerance including vomiting, excessive gastric aspirates, and abdominal distension.[68, 69]

The main existing treatment options:

UCSF Benioff Children's hospital, San Francisco Intensive Care Nursey recommended a detailed treatment algorithm and guidelines reflecting consensus of Neonatology, Paediatric Surgery and Antimicrobial Stewardship services based on available evidence.

The recommended antimicrobials for suspected cases of NEC were combination of Nafcillin and Gentamicin. The neonates with history of MRSA colonization were recommended to treat with Vancomycin plus Gentamicin. The treatment was discontinued based on clinical evolution/suspicion of infection post 48h or a defined course of sepsis lasting from 5-7 days was recommended.

For definite NEC cases, based on clinical symptoms, a combination of Ampicillin, Gentamicin and Metronidazole or a combination of Piperacillin and Tazobactam was recommended. The usual duration of antimicrobial treatment for definite cases of NEC was 7 days.[70]

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

Mortality

A systematic review that analysed data from 131 articles published between January 1980 and September 2022 reported a mortality rate of 8% (n=20) among 242 infants ≤3 months of age with appendicitis.[71]

The 7-day mortality rate of NEC in a retrospective Swedish study from 2005 to 2009 was 1.27 per 1,000 live births.[66] The 10-year mortality rate in pre-term infants with NEC in Spain was 14.5% (3,738 deaths of 25,821 infants).[65]

Morbidity

The rate of morbidity, as defined by postoperative complications Clavien - Dindo [CD] grades I – IV, in infants ≤ 3 months of age with appendicitis was 8% (n =18 out of 242 cases).[71] Neonates diagnosed with appendicitis undergo surgical treatment, which can cause post operative complications such as SSIs, slow peristalsis, adhesive ileus, wound dehiscence, catheter-related sepsis, and intestinal perforation.[71]

Important co-morbidities

Important co-morbidities in neonates with appendicitis are cardiorespiratory failure, inguinal hernia, and Hirschsprung's disease.[72] The co-morbidities in neonates with NEC are bronchopulmonary dysplasia, late-onset sepsis, cystic periventricular leukomalacia, retinopathy of prematurity, and acute kidney injury.[65]

SI.2. Indication: Complicated Urinary Tract Infection, Including Pyelonephritis

A review of the literature was conducted using MEDLINE via PubMed to identify non-interventional studies conducted among the adult population diagnosed with cUTI from January 2019 to August 2023. Search terms included (incidence, prevalence, epidemiology, mortality, morbidity, comorbidity or risk factors) and (complicated urinary tract infections). The search also included common sources of cUTI such as acute pyelonephritis.

A similar approach of literature search was applied for paediatric and neonatal population. For neonates, considering paucity of the epidemiology studies, search frame was expanded to the last 10 years (beginning January 2014).

SI.2.1. Indication: Complicated Urinary Tract Infection, Including Pyelonephritis (Adult Population)

Incidence:

A UTI is a bacterial infection of predominantly the lower organs (acute cystitis) or, more rarely, the upper renal pelvis and kidney (acute pyelonephritis).[73] 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 co-morbidities.[74-76] Some investigators consider any UTI in patients more than 65 years of age or in men at any age to be a cUTI.[76, 77] Catheter-associated UTI (CA-UTI) is also most often studied as a subset of cUTI.[78] The US Food and Drug Administration (FDA) considers pyelonephritis as cUTI in the absence of other complicating factors.

Globally, the pooled incidence of UTI among patients admitted to the health facility was 1.6% (95% CI: 1.3- 2.4), as reported in a systematic review and meta-analysis including data of 38 studies from 26 countries worldwide on 981,221 patients.[79]

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 for cUTI.[80] The estimated annual incidence of cUTI was 1.14% among US adults, equating to over 2.8 million cases of cUTI per year.[80] Women have a higher incidence of cUTI (ranging from 1.20% to 1.42%) than men until age 55 (ranging from 0.13% to 0.71%). In patients aged ≥ 65, men's incidence of cUTI exceeded women's rate (3.06% vs. 1.77%).[80]

A large perspective study in 141 hospitals from 25 European countries reported an incidence of nosocomial UTIs of 3.55 cases per 1,000 patient days in 2000.[81]

In an observational study conducted among patients with cUTI, 17% of patients had the presence of a urinary catheter in Netherlands.[82] However, the incidence of CA-UTI varies

considerably by region and treating unit within the hospital in Netherlands (range 0.50 to 15 per 1,000 catheter-days).[83]

Prevalence:

A prospective, multicenter study (May to June 2002) conducted on over 13,000 urology outpatients in Italy reported prevalence of cUTI of 10.8% (1,201 cUTI cases).[74] Inter-regional differences in the prevalence reported in the same study did not demonstrate statistical significance (South/Islands 12.2%; Centre 11.4%; and North 8.4%). The prevalence of nosocomially acquired UTI in a large European population was 10.65 episodes per 1,000 patients in 2000.[81] A global prevalence study of infections in urology from 2003 to 2010 estimated a prevalence of nosocomially acquired UTIs of 9.4% (1,866 UTI cases out of 19,756 urology patients).[84]

A point prevalence survey in European acute care hospitals of all EU Member States, Norway, Iceland and Croatia in 2011 – 2012 found a prevalence of UTI of 19% among 15,000 HAIs.[85]

In the US, cUTI comprised approximately 1.8% (626,520 cUTI cases) of 35,527,481 annual hospital admissions, as reported by a cross-sectional analysis of the 2018 NIS database.[78]

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

Age, gender, and race/ethnicity

cUTI can occur in any age group but are more common among the elderly. The mean age reported in two observational studies conducted among patients with cUTI was 62 years.[74, 82] More than 70% of the hospitalized patients with cUTI were ≥65 years of age in an analysis based on NIS in the US.[78] The median age of hospitalized patients with cUTI ranged between 68-71 years in a multicenter, retrospective observational study in Southern Europe, Turkey, and Israel (COMBACTE - MAGNET RESCUING study) from January 2013 to August 2014.[86] The patients who belonged to the age group 65-84 years had the highest chances of developing CA-UTI, (47.79% (60,275 of 126,115 CA-UTI cases)) followed by patients with age more than 85 years (22.18% (27,970 of 126,115 CA-UTI cases)) and 55-64 years (15.04% (18,965 of 126,115 CA-UTI cases)).

cUTI occurs in both sexes; however, they have been reported more frequently among females compared with males. UTIs among males are considered complicated by some experts.[76] In previously conducted clinical and observational studies among patients with cUTI, the proportion of females reported has ranged from 38% to 78%.[74, 82, 87, 88] The recent studies also reported the proportion of females ranging from 33.61% to 68.07%, demonstrating consistent gender distribution over the time.[78, 80, 86]

According to the NIS study in US, White race demonstrated highest prevalence of CA-UTI (70.92% [89,445 of 126,115 cases]) followed by Black (14.05% [17,725 of 126,115]) and Hispanic races (8.13% [54,875 of 126,115 cases]).[78]

In studies, pyelonephritis was reported among a majority (range 40% to 53%) of patients with cUTI.[87, 88]

Risk factors

Risk factors related to cUTI can be broadly classified into structural and functional abnormalities.[76, 89-91] Obstruction due to stones or tumours 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.[75, 92] 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.[91, 93] The risk factors associated with catheter-associated cUTIs were age greater than or equal to 65 years, male gender, and increased duration of hospital admission.[86]

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* (e.g., a fluoroquinolone [if not already used], an acylaminopenicillin with a BLI, a Group 3b cephalosporin, or a carbapenem with or without an aminoglycoside).[94] The choice of antibiotic treatment depends on the pathogen and local susceptibility patterns.

Additionally, the risk of Multi Drug-Resistant (MDR) 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.

The treatment options recommended by Michigan Hospital Medicine Safety Consortium for complicated lower urinary tract infections or cystitis are nitrofurantoin for 7 days, or Fosfomycin Q 48h in 3 to 5 doses, or IV or oral β-lactam or aztreonam (in case of β-lactam allergy) for 7 days.[95]

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

Mortality

According to the NIS study in the US, non-CA-cUTI patients reported lower hospital mortality (2.8%) compared to patients with CA-UTI (3.4%), indicating risk of fatal nosocomial infections associated with the use of catheters in UTI patients.[78]

The 30-day mortality rates in the CA-cUTI group were 15.2% (52 of 341) and 6% in the other cUTI group, as reported by the COMBACTE-MAGNET RESCUING study in twenty hospitals from eight countries from Southern Europe, Turkey and Israel.[86] This was consistent with findings from a prospective observational study (N=1,325) conducted among patients with complicated pyelonephritis with reported crude mortality rate of 6.5% and attributable mortality of 4.1%.[96]

In two observational studies from Asian region conducted among patients with cUTI, mortality rates reported ranged from 2% to 4%.[87, 97]

This was slightly higher than the mortality rate reported in the Leiden 85-plus study (1.1% [7 deaths during follow-up of four years due to UTI in 599 enrolled patients]).[98]

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.[76] Fever, rigours, nausea, vomiting, anorexia, and Diarrhoea may occur with upper UTIs. Recurrent infection and increased antimicrobial resistance are additional risks.[99]

By definition, cUTI involves a subset of patients with more inherent risk (e.g., an anatomically abnormal urinary tract or a significant medical comorbidity) or more acquired risk (e.g., 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.[75] 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.[73] Besides suppurative complications, UTI may be associated with bone, joint, or heart tissue infection.[76]

Important co-morbidities:

For the indication of complicated urinary tract infections (including pyelonephritis), the important comorbidities are diabetes,[74, 75, 92, 100-102] stroke,[103-107] hypertension, cardiac arrhythmias, renal failure, fluid and electrolyte disorders, neurodegenerative disorders, congestive heart failure, chronic pulmonary diseases.[78, 80]

SI.2.2. Indication: Complicated Urinary Tract Infection including pyelonephritis (Paediatric Population)

Data on the incidence of cUTI in children were scarce because most UTI cases are considered as uncomplicated in otherwise healthy children.[108] UTI is a common clinical problem in paediatric population in which an estimated 7.8% girls and 1.7% boys would experience at least one episode before reaching 7 years old.[109-111] For infants less than 1 year old, the incidence of UTI was 0.7% in girls and 2.7% in uncircumcised boys.[112-115] Girls are more likely to develop UTI than boys after the first one year of life.[116-120]

Prevalence:

Vesicoureteral reflux is the most commonly seen urological abnormality in children. It may increase risk of UTI in children and renal scarring, also known as reflux nephropathy (chronic pyelonephritis) – a subtype of cUTI, which is of more complex pathology than acute pyelonephritis.[121] The prevalence of vesicoureteral reflux is estimated to be 0.4%–1.8% of the paediatric population who have not presented with urinary tract infections (UTI), and 10%–40% in patients who have presented with UTI.[122] A systematic review of 33 studies of 4,891 children after an initial episode of UTI, the prevalence of acute pyelonephritis was 57% and renal scarring was 15%.[123] It was also noted that the annual incidence of UTI recurrence was between 5% to 11% in children after an initial UTI.[123]

In a large systematic review and meta-analysis, the pooled prevalence of UTI in children older than 2 years of age was 7.8% (95% CI: 6.6–8.9%) and in infants less than 24 months of age was 7.0% (95% CI, 5.5-8.4%).[124]

The overall pooled prevalence of UTI in febrile children ranged from 5.5% to 8.4%, as reported in a systematic review that contained 18 studies evaluating 22,919 children (17 studies from USA and 1 study from Taiwan).[124] In contrast, malnourished children had higher prevalence of UTI of 17% (95% CI: 13-21%), as reported by another global systematic review and meta-analysis on 3,294 malnourished children.[125]

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

<u>Age, gender, and race/ethnicity</u>

cUTI can develop at any age and in both sexes, and its epidemiology varies with age, sex, and race.[108]

The cumulative incidence rates for boys and girls were 3.45% and 4.14%, respectively, for the first year of life. However, girls reported 5.7 times higher prevalence than boys (11.8% vs 6.81%) for one to six years, indicating age-dependent UTI incidence, as reported by a population-based study that assessed 1,049 infants between October to December 2004 and April to July 2015 in Greece.[126]

Children less than 19 years reported pooled UTI prevalence of 7.8% regardless of their febrile condition.[124] A systematic review assessing relationship between race and UTI in

17,845 children from 11 studies found that non-black children reported 2.44 times higher odds of developing UTI compared to black children (95% CI: 3.16-7.41; I2 = 0%).[127]

Risk factors

The risk of cUTI is increased in patients with upper urinary tract obstructions, secondary to various causes (eg., stones, tumours and ureteropelvic junction obstructions).[108] Other predisposing factors include presence of a functional or anatomical abnormality of the urinary tract, especially high-grade VUR or severe urinary tract obstruction at any level; the presence of an indwelling urethral catheter, stent, percutaneous nephrostomy tube or other urinary diversion; recent urinary tract instrumentation; broad-spectrum antimicrobial resistant uropathogen; hospital acquired infection; renal failure; renal transplantation; and immunosuppression.[108] The risk also increases with malnourishment, inadequate fluid intake, decreased frequency of voiding, low vitamin D levels, and obesity[128] and lack of circumcision.[129] The most common causative microorganisms are *Escherichia coli*, *Klebsiella pneumonia*, *Klebsiella oxytoca*, and *Proteus mirabilis*.[130]

The main existing treatment options:

As in adults, the choice of antibiotic treatment depends on the pathogen and local susceptibility patterns.[116]

For paediatric patients, the combined guidelines from the European Association of Urology and the European Society for Paediatric Urology include the following parenteral treatment recommendations for a range of paediatric urinary tract infections: cephalosporins (eg., cefotaxime, ceftazidime, ceftriaxone), ampicillin, amoxicillin/clavulanic acid, piperacillin, ciprofloxacin and aminoglycosides (tobramycin, gentamicin). Intravenous treatment is generally recommended for a range of 1 to 3 days, depending on the specific agent, followed by step-down oral treatment, which may include oral cephalosporins (ceftibuten, cefixime, cefpodoxime proxetil, cefuroxime axetil, cefaclor), trimethoprim, trimethoprim/sulfamethoxazole, amoxicillin, amoxicillin/clavulanic acid, ciprofloxacin, or nitrofurantoin.[116] For treatment of pyelonephritis requiring intravenous therapy, combinations of ceftazidime and ampicillin or an aminoglycoside and ampicillin are recommended for between 3 and 7 days (depending on age) followed by step-down oral treatment.[116]

Antibacterial Management:

The decisive factors regarding treatment using either oral or parenteral routes for urinary tract infections (UTIs) included patient age, clinical suspicion of urosepsis, and the presence of complications like vomiting, diarrhoea, and complicated pyelonephritis. Due to high susceptibility of newborns and infants under two months old to urosepsis and severe pyelonephritis, parenteral antibiotic treatment is recommended in this age group. It was studied that shorter courses (1-3 days) were less effective than longer courses (7-14 days).

In case of ambulatory treatment in complicated UTIs with chances of involvement of alternative pathogens, close monitoring and potential adjustments was found necessary with a possibility to temporarily perform urinary diversion in obstructive uropathy cases. Additional

factors to consider while choosing antibiotics for UTI were local resistance patterns, patient history, and individual characteristics.[131]

Prophylactic Management:

The prevention of recurrent UTIs may stop development of renal scarring. Although chemoprophylaxis could be commonly used, rising resistance rates to it was shown as an important concern. It was also found unsuccessful in preventing renal damage, except in children with urinary tract abnormalities. The intravesical application of gentamicin could be effective in a few cases. However, dietary supplements like cranberry juice and probiotics were recommended, especially in children with urogenital abnormalities. The use of steroid cream in boys demonstrated reduced rates of recurrent UTIs in boys with physiologic phimosis. Also, circumcision was found to be an effective prophylactic intervention against UTIs in newborns with anatomical abnormalities. Moreover, the need for bladded and bowel dysfunction (BBD) screening and subsequent treatment was considered to be of great importance to lower UTI recurrence.[131]

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

Mortality

Paediatric mortality due to UTI in otherwise healthy children is rare in developed countries.[132, 133]

Morbidity

In general, paediatric patients with cUTI are more severely ill, may present with sepsis, multiple organ-system dysfunction, shock and/or acute renal failure. Some paediatric patients may experience a cUTI, comprising acute pyelonephritis complicated by papillary necrosis, emphysematous pyelonephritis, pyonephrosis, renal abscess and perinephric abscess.[108] Paediatric patients with cUTI can fail to respond to conservative treatment (such as antibiotic treatment, hydration, antipyretic and rest), and may need surgical intervention to treat (e.g., insertion of percutaneous nephrostomy or abscess drainage).[108] High recurrence rates, malformation of the urinary tract, and renal scarring also contribute to the morbidity of cUTI.[126]

Important co-morbidities:

Important co-morbidities of cUTI among paediatric patients include congenital anomalies of the kidney and urinary tract, abnormalities of the genitourinary tract, diarrhoea, gastroenteritis, respiratory diseases, and sepsis of bacteraemia.[112, 125, 134]

SI.2.3. Indication: Complicated Urinary Tract Infection including pyelonephritis (Neonatal Population)

Neonates and infants with UTI are more prone to develop acute morbidity and long-term renal insufficiency due to high association between urinary tract malformation and

concurrent bacteraemia. This makes their UTIs more complicated in terms of treatment and management.[115]

Incidence:

An accurate incidence of UTI among neonates and infants < 3 months old is difficult to assess due to the inclusion of broader age groups in most studies.[135]

A retrospective medical records review of 670 febrile neonates younger than 30 days of age reported 100 new cases of UTI (15.4%) during a 10-year period in a medical centre in New York, USA.[136] This was in line with the incidence range (3.5% - 17.8%) reported by a prior retrospective chart review of 207 patients with urine culture positive indicative of UTI in infants younger than 60 days of age.[137]

Prevalence:

UTI in infants < 3 months old accounted for 21% of all children with first UTI diagnosis.[138] In a systematic review and meta-analysis, the pooled prevalence of febrile UTI in female infants aged < 3 month old was 7.5%; among male infants < 3 months old, the prevalence was 2.4% in circumcised males and 20.1% in uncircumcised males.[124]

In neonates 2-14 days old with unexplained indirect hyperbilirubinemia, the prevalence of UTI was 12.2% (32 UTI cases in 262 neonates). Among 77 febrile neonates aged between 0 to 2 months, the frequency of UTI was 12.99% (10 UTI cases in 77 neonates)[139] (Table 13).

Table 13. Prevalence of urinary tract infections in neonatal population

Sr No	Author Year	Sample Size	Design	Prevalence	Country
1	Ismaili K 2011[138]	209 children with first UTI diagnosis	Prospective observational study from July 2006 to July 2008	21% (43 infants aged between 0 to 3 months of 209 children diagnosed with UTI) UTI occurred in aged 0-3 months	Belgium
2	Bahat Ozdogan E 2018[140]	262 neonates aged between 2 to 14 days diagnosed with hyperbilirubinemia	Prospective study from November 2004 to November 2007	12.2% (32 neonates diagnosed with UTI of 262 neonates with hyperbilirubinemia)	Turkey
3	Saad M 2023[139]	77 febrile neonates aged between 0 to 2 months	Cross-sectional study conducted in NICU and outpatient clinic from April 2017 to April 2018	12.99% (10 UTI patients of 77 febrile neonates)	Egypt
4	Shaikh N 2008[124]	22,919 febrile infants	Systematic review and meta-analysis of articles from January 1966 to October 2005	Pooled prevalence of UTI: Among female infants aged <3 months: 7.5%Among circumcised male infants < 3 months of age: 2.4% Among uncircumcised male infants < 3 months of age: 20.1%	Global

NICU = Neonatal Intensive Care Unit; UTI = Urinary Tract Infection

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

Age, gender, and race/ethnicity

Mean age was 40 ± 29 days in young infants < 3 months of age, as reported by a prospective study conducted in Belgium on 209 young patients with UTIs.[138] The proportion of male gender ranged from 59% (19 of 32 UTI positive neonates) to 74% (32 of 43 neonates with first UTI), in prospective studies on Turkish and Belgian neonates with UTIs.[138, 140] In general, there is a male predominance for neonatal UTI. Higher prevalence of febrile UTI in male infants < 3 months of age (8.7% [95% CI, 5.4-11.9%]), was reported than female infants of same age group (7.5% [95% CI, 5.1-10.0%]). Also, the prevalence of febrile UTI in White infants was 8.0% (95% CI, 5.1-11.0%), which was higher than that in Black infants, 4.7% (95% CI, 2.1-7.3%).[124]

Risk factors

The risk factors associated with cUTI in neonates are presence of VUR, male gender, uncircumcised state, and renal abnormalities. UTI in neonates is most commonly caused by *Escherichia. Coli.*[138]

The main existing treatment options:

According to the European Association of Urology guidelines on management of UTI in children, the precursor interventions to the onset of antimicrobial regimen included urinalysis and urine culture. A pyelonephritis treatment algorithm recommended use of ceftazidime and ampicillin or aminoglycoside and ampicillin for 10 to 14 days during the first 6 months or disease via parenteral administration for 7 to 14 days followed by oral therapy.

Similar treatment regimen was recommended for complicated pyelonephritis treatment (ceftazidime and ampicillin or aminoglycoside and ampicillin for 10 to 14 days via parenteral for 7 days followed by oral therapy).[116]

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

Mortality

Mortality rate for cUTI, UTI, or associated infections in neonates were not reported in the retrieved articles.

However, it is evident that the mortality rate in infants with and without candidiasis was 34% (47 deaths of 137 infants with candidiasis) and 14% (197 deaths of 1378 infants without candidiasis), respectively, as reported by a prospective observational cohort study on infants <1000 g birth weight at 19 centres of the NICHD Neonatal Research Network, USA.

Morbidity

Neonatal UTI may result in late-onset sepsis and likelihood of candidiasis in neonatal ICU (NICU).[141] Other important morbidities associated with neonatal UTI are asthma, allergic rhinitis.[141, 142] Recurrent urinary infections may lead to severe kidney damage in neonates such as renal parenchymal scarring and chronic kidney disease.[143]

Important co-morbidities

The underlying renal abnormalities which can contribute to neonatal UTI are VUR,[144] jaundice and unexplained hyperbilirubinemia, and bacteraemia.[135]

SI.3. Indication: Hospital-Acquired Pneumonia (HAP) including Ventilator-Associated Pneumonia (VAP)

Hospital-acquired pneumonia (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; "Non-VAP" identifies as patients who do not have VAP.[145, 146]

While NP is any case of pneumonia that occurs after at least 48 hours in a chronic care or inpatient acute facility or within 7 days of discharge from one of these facilities, and HAP is any case of pneumonia that occurs in a patient who has been hospitalised more than 48 hours, Pfizer considers NP to be broadly similar clinically to HAP and therefore will use NP and HAP interchangeably within this Risk Management Plan (RMP).

A search of the literature was conducted using MEDLINE via PubMed to identify non-interventional studies conducted among the adult population diagnosed with HAP/VAP published from January 2019 to August 2023. Search terms included (incidence, prevalence, epidemiology, mortality, morbidity, comorbidity or risk factors) and (HAP/VAP).

A similar approach of literature search for paediatric and neonatal population was applied. For neonates, considering paucity of the epidemiology studies, literature search was expanded to the last 10 years (beginning January 2014) and also included common sources of HAP/VAP in neonates such as neonatal sepsis.

SI.3.1. Indication: Hospital-Acquired Pneumonia (HAP) including Ventilator-Associated Pneumonia (VAP) (Adult Population)

Incidence:

The global incidence of HAP varies from 5 to more than 20 per 1,000 hospital admissions.[147] One-third of HAP cases are considered ICU acquired, and the majority of them are VAP.[145, 148] The incidence of HAP is highest among immunocompromised, surgical and older patients.[148]

In the US, the estimated incidence of VAP ranges from 2 to 6 cases per 1,000 ventilator-days and incidence of non-ventilator HAP is 3.63 per 1,000 patient days.[149] The average 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).[149] 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 1,000 patient days; the median length of stay for patients with non-ventilator HAP was 16 (interquartile range: 11-26) days.[150] The incidence of VAP in the European countries appears much higher in ICU patients, exceeding 18 per 1,000 ventilator-days.[151]

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.[145]

Prevalence:

A point prevalence survey of 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.[152] 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 European ACH. 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.[152]

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 European countries. Patients with long hospital stay, old age and men had a high prevalence of HAP. The prevalence of HAP in Europe varied from 0.6% (95% CI, 0.2–1.4) in Latvia to 3.7% (95% CI, 1.0–12.3) in Iceland.[153]

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.[154]

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[155] and 25.8% (n=110) in 2015.[154]

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.[155] 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).[154]

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

Age, gender, and race/ethnicity

Data from 2012 US National Inpatient Sample suggest that 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.[149]

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 61 years 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.[156] The proportions of Black and Hispanic in non-ventilator HAP patients were 75% male. 12.7% and 3.3%, respectively, and 17.7% and 3.9%, respectively, among VAP patients.

Risk factors

Risk factors associated with HAP are summarised in Table 14.

Table 14. Risk factors for the Development of Hospital-Acquired Pneumonia

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:[157, 158]

Key risk factors/predictors for high risk of mortality in VAP/HAP patients included creatinine level, fever, malignancy, congestive heart failure, APACHE II score, old age, appropriate empiric antimicrobial treatment, use of vasopressor, Charlson Comorbidity Index

(CCI), total antibiotic treatment days, COVID-19 infections and recent history of surgery.[159-162]

The main existing treatment options:

Guidelines

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. However, patients with NP due to *P. aeruginosa* may require longer drug administration ranging from 14 to 21 days.[145, 163, 164]

European guidelines recommend antibiotic treatment for HAP no longer than 7 days. However, the duration of therapy for multidrug-resistant organisms (MDROs) is not clearly established.[165]

The table below summarises the antibiotics recommended in the empirical management of HAP.[166]

Table 15. 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.

Source:[166]
HAP = Hospital-Acquired Pneumonia

A publication presented guidance on the treatment of NP based on a task force of scientific personnel from three European Societies: The European Respiratory Society, European Society of Clinical Microbiology and Infectious Diseases, and European Society of Intensive Care Medicine.[167] 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.[167]

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.[168] The estimated global mortality due to HAP is 20-30% and the mortality due to VAP is 20-50%.[168]

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%.[149, 156] 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).[149] In another large study in the US using electronic surveillance criteria, the crude inpatient mortality was 22.4% for patients with non-ventilator HAP.[150]

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.[169]

Important co-morbidities:

For the indication of HAP hospital-acquired pneumonia (including VAP), the important co-morbidities are cardiac disorders,[170] hypertension,[156] pulmonary disorders,[171] nephrotoxicity/renal dysfunction,[172-176] congestive heart failure, neurological disorders, diabetes, liver disease, coagulopathy, cancer, and depression.[156]

SI.3.2. Indication: Hospital-Acquired Pneumonia (HAP) including Ventilator-Associated Pneumonia (VAP) (Paediatric population)

Incidence:

Individual observational studies conducted among paediatric patients report HAP incidence rates with ranges from 0.6 to 0.9 per 1,000 patient days in Germany to 13 per 1,000 patient days in Brazil and Egypt.[177-180] Globally, incidence rate for VAP was estimated from the INICC surveillance study from 2010 to 2015 in ICUs from 50 countries from Latin America, Europe, Eastern Mediterranean, Southeast Asia, and Western Pacific World Health Organization regions.[181] The pooled mean VAP incidence rates were 8.2 per 1,000 mechanical ventilator-days in PICUs.

Surveillance for VAP has shifted towards a broader category of ventilator-associated events (VAE).[182] In an updated INICC surveillance study from 2013 to 2018, the pooled mean incidence rate of VAE was 15.61 per 1,000 ventilator-days.[181] Individual observational studies conducted in paediatric ICU (PICUs) reported VAE incidence rates ranging from 8.55 per 1,000 ventilator-days in Spain to 9.7 per 1,000 ventilator-days in northern Greece.[183, 184]

In the US, the mean VAP rate in a PICU was 11.6 per 1,000 ventilator-days, as reported in a review.[185]

The mean VAP rate was 8.87 per 1,000 ventilator-days, as reported by a prospective study of VAP among all 361 patients that received mechanical ventilation for 48 hours and more in a PICU in Saudi Arabia from May 2000 to November 2002.[186]

Variations in incidence rates can be due to differences in study methodology, patient population, case definitions, and institutional practices.[187]

Among children with VAP, the microorganism type and antibiotic susceptibility are variable according to the geographical region.[188] Gram-negative pathogens predominate, but their contribution is exceptionally high in Asia.[188]

Overall, the most common pathogens are *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Enterobacteriacea*e.[188] In Europe and North America *Staphylococcus aureus* predominate. In Asia, most pathogens are multidrug-resistant.[188]

Prevalence:

The European Multicenter Study Group found pneumonia, at 53% of all infections, to be the most common nosocomial infection in PICU.[189]

No epidemiologic data specifying prevalence of HAP including VAP among children were identified.

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

Age, gender, and race/ethnicity

Specific differences in literature are not reported by age and sex, but HAP is a common infection, particularly in neonates and children who require intubation or intensive care support, and those with underlying chronic illnesses.[187] In a prospective cohort study of children under 18 years of age (n=765) from a PICU, the majority of patients with HAP were under 24 months of age (57%) compared to 24 months and over and were mostly female (55%).[178] In a study of 90 patients admitted to the PICU, those diagnosed with HAP had a mean age of 22 months and 76% were male.[179]

Risk factors

Risk factors for HAP among children include admission to an ICU, intubation, burns, surgery, and underlying chronic illness.[187] Post-surgical admission diagnosis, subglottic or tracheal stenosis, prolonged ventilation, reintubation, tracheostomy, bronchoscopy, enteral feeding, and prior antibiotic therapy are some of the factors that have been reported in the development of VAP.[188]

The main existing treatment options:

Treatment of HAP/VAP in children requires coverage for *Staphylococcus aureus*, *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and, less frequently, anaerobes.[187, 190] Aminoglycoside based regimens are generally recommended when the causative pathogens are suspected to be extended-spectrum-beta-lactamases (ESBL)-or Amp-C producing Gram-negative bacteria. Potential treatment options include an aminoglycoside (e.g., gentamicin or amikacin) in combination with one of the following: piperacillin-tazobactam, meropenem, ceftazidime, cefepime, or clindamycin. When methicillin-resistant *Staphylococcus aureus* is a consideration, it is recommended that vancomycin be added to the empiric treatment regimen, using an agent other than piperacillin-tazobactam (since the combination of these 2

drugs may result in increased risk of acute kidney injury). For hospital-acquired aspiration pneumonia, recommended therapies include piperacillin-tazobactam or meropenem.[190, 191]

A diagnosis and management plan for HAP/VAP in children (empiric and definitive) delineated by majority antibiotic stewardship (2021) programmes included mainly cefepime, vancomycin, or linezolid, trimethoprim-sulfamethoxazole, ceftaroline and clindamycin. To expand Gram-negative coverage, meropenem or aminoglycosides were recommended. [192-194]

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

Infants and children are widely recognized to be susceptible to viral pathogens causing lower respiratory tract infection, with documented nosocomial spread.[195]

Mortality and Morbidity

VAP results in increased morbidity and mortality rates, hospital length of stay, and healthcare costs.[196] For instance, in a retrospective cohort study of 127 patients in the PICU, those diagnosed with VAP had a median hospital length of stay of 19 days compared to 5 days in those without VAP.[197]

Observational studies have documented an increase in mortality among a paediatric population with HAP or VAP with a range of 10.5% to 44%.[179, 198-200] In a cohort study from Italy, 1446 children admitted in the PICU, of which 451 were mechanically ventilated children.[198] Among children with VAP the mortality was 16.7% compared to 5.9% among those without VAP.[198]

Statistically significant differences between the VAP and non-VAP children in this study included higher percentage of VAP patients who had previous non-invasive ventilation, reintubation, enteral nutrition, and longer length of hospital stay.[198]

Important co-morbidities:

Important co-morbidities among children with HAP (including VAP) include neonatal chronic lung disease, congenital anatomic or acquired cardiopulmonary disease and frequent respiratory tract viral infections.[195]

SI.3.3. Indication: Hospital-Acquired Pneumonia (HAP) including Ventilator-Associated Pneumonia (VAP) (Neonatal Population)

Incidence

Globally, a surveillance study from INICC conducted across 50 countries from 2010 to 2015 estimated that the mean incidence rate of VAP was 9.02 events per 1,000 ventilator-days among mechanically ventilated infants in the NICU.[201] In individual European studies, the incidence of VAP in NICU ranged from 10.47 per 1,000 ventilator-days in UK to 35.06 per 1,000 ventilator-days in Bulgaria. There were large variations in VAP incidence rates in

NICU, which was heavily influenced by gestational age and economic status of the region, and potentially variations of VAP definitions used.[202]

Prevalence

VAP is common in NICU, and the burden of VAP is often estimated by incidence in the literature, as described above. Limited data exist for the prevalence of VAP. It has been reported that VAP accounted for 6.8% to 57.0% of HAIs in NICU.[188]

A prospective observational study in 198 newborn infants with VAP reported that VAP prevalence was 8.1%.[202, 203]

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

Age, gender, and race/ethnicity

The proportion of males in neonates with VAP was 67% in both of the Bulgarian and UK observational studies. The mean gestational age was 31.08 weeks (SD 4.83) in the Bulgarian study and 25 weeks (SD 2.8) in the UK study.[188] Race/ethnicity data were not reported in those studies.

Risk factors

Low birth weight, lower gestational age, and prolonged mechanical ventilation are main risk factors for VAP. Other risk factors include timing of ventilation, opiate treatment for sedation, frequent suctioning and reintubation, bloodstream infection, enteral feeding and parenteral nutrition, and bronchopulmonary dysplasia, as reported by the World Health Organization VAP treatment operational guidance 2018.[204, 205]

The main treatment options:

VAP prevention bundle strategies are the most recommended approach to treat VAP in newborn infants. It includes healthcare professional training to all healthcare providers, adherence to hand hygiene guidelines and correct use of sterile gloves prior to the management of ventilation equipment/supplies, sterile management of airway including total barrier prevention strategies to be employed during endotracheal intubation and surfactant administration, avoidance of reintubations, oral care, positioning to decrease gastric micro aspirations, tube feeding, and caring of the ventilator-circuit. Antibiotic treatment will be based on clinical diagnosis and judgement on an empirical basis or specific case-to-case basis.[206]

Natural History of the proposed indicated condition in the untreated population, including mortality, morbidity and risk factors:

Mortality

Globally, a surveillance study from INICC from 2010-2015 reported a pooled crude mortality rate of 28.4% (95% CI, 18.5-40.0%) for neonates with VAP at NICU.[201] The mortality rate for neonates with VAP was 9% (3 of 33) in the Bulgarian study and 23.8% (5 of 21) in the UK study.[188]

Morbidity

VAP is associated with significant morbidity due to prolonged requirement of ventilation and length of hospital stay. For example, the average stay of patients with VAP in the NICU was statistically significantly longer than the hospital stays of non-VAP patients (35.70 ± 21.84 days vs. 21.77 ± 17.27 days; p = 0.002). In neonates with VAP, the duration of mechanical ventilation was statistically significantly longer compared with non-VAP patients (16.88 ± 11.99 vs. 5.42 ± 4.48; p = 0.000). VAP also put neonates at increased risk of developing a subsequent episode of HAI.[204, 205, 207]

Important co-morbidities

Important co-morbidities among the neonates with VAP include bronchopulmonary dysplasia, hyaline membrane disease, bloodstream infections (BSIs), and necrotizing enterocolitis.[208]

SI.4. Indication: Infections due to Aerobic Gram-negative Organisms in Patients with Limited Treatment Options

CAZ-AVI is indicated for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options.[209]

In the face of increasing global antibiotic resistance, there are limited remaining therapeutic options for the treatment of resistant Gram-negative pathogens. There is an urgent need for new antibiotics to treat serious Gram-negative infections proven or suspected to be caused by β-lactam-resistant pathogens, including those producing ESBLs.

This unmet need spans different infection types, including cIAI, cUTI and HAP, but also other serious Gram-negative infections where patients have limited treatment options either due to resistance or due to an inability to tolerate existing therapies.

Treatment options for resistant Gram-negative pathogens are also limited by the tolerability of alternative antibiotic therapies. In the absence of new therapeutic agents for serious Gram-negative infections and in light of rising resistance to carbapenems, clinicians are increasingly forced to turn to drugs that had previously fallen out of favour due to associated toxicity.[210] Therapies for use in the MDR and extensively drug-resistant setting, for example, include colistin and tigecycline.[211] Colistin's potential for nephrotoxicity and tigecycline's connection with increased rates of mortality limit their use as therapeutic alternatives.

Several new agents against certain carbapenem-resistant pathogens have been approved recently for their clinical use or are reaching late-stage clinical development. They include CAZ-AVI, ceftolozane-tazobactam, meropenem–vaborbactam, imipenem-cilastatin-relebactam, plazomicin, eravacycline, and cefiderocol.[212] Besides, fosfomycin's redevelopment is also in progress in form of a new intravenous formulation.

Current preliminary data from clinical trials on the clinical efficacy and safety of these new agents specific to infections caused by carbapenem-resistant pathogens is suggestive of superiority of newer agents' over previous best available therapy. However, this also calls for a robust antimicrobial stewardship to ensure appropriate and rational use of newly developed agents against GMN bacteria in benefit of patient community.[212]

For the identification of multidrug-resistant bacterial infection-related epidemiology studies for adult, paediatric and neonatal population, relevant search terms such as MDR, ESBL-producing bacteria, limited treatment options, and aerobic gram-negative bacteria, neonatal sepsis, and bacteraemia using MeSH and text words in MEDLINE via PubMed were used with a search window of last 10 years (January 2014 to August 2023).

SI.4.1. Indication: Infections due to Aerobic Gram-negative Organisms in Patients with Limited Treatment Options (Adult Population)

Incidence:

Resistance in bacterial pathogens is a function of immediate environmental differences and thus varies by geographic area, hospital, ward, and patient over time. Estimates also vary by method of detection, sampling and testing strategy, and publication and reporting bias.[213]

Resistance trends from any given regional, national, or international surveillance study cannot long be a reliable measure of the epidemiology of constantly changing Gram-negative susceptibility patterns.[214] However, a trend towards increased resistance amongst Gram-negative bacilli is commonly reported in regional and international studies. From 2002 to 2010, an international survey of IAIs reported ESBL-producing properties in 6% to 33% of *Klebsiella* species.[215]

A cohort study of 890 US hospitals between 2012-2017 identified that the incidence of ESBL infection was increased by 53.3% (from 37.55 to 57.12 cases per 10,000 hospitalisations) due to an increase in community-onset infections.[216]

From 2002 to 2004, all hospitalised patients colonised or infected with multidrug-resistant Gram-negative (MRGN) bacteria identified in a single German study were prospectively followed. During the 3-year study period, 503 case-patients (351 different patients) were identified for an overall MRGN incidence of 0.43 case-patients per 1,000 patient days.[217] ESBL-producing bacteria were detected at an incidence of 0.12 case-patients per 1,000 patient days. A prospective study capturing data of a German hospital from 2014 to 2015 reported that incidence rate for HAI caused by ESBL-producing *enterobacterales* (ESBL-E) was 2.74 per 1,000 patient days (95% CI: 2.16-3.43) among carriers of ESBL-producing *Escherichia coli* (ESBL-EC), while it was 4.44 per 1,000 patient days (95% CI: 3.17-6.04) among carriers of ESBL-producing *Klebsiella pneumoniae* (ESBL-KP).[218]

As part of the antimicrobial susceptibility Study for Monitoring Antimicrobial Resistance Trends (SMART) covering Spanish hospitals in 2002 to 2010, 8,869 Gram-negative samples isolated from IAIs were tested for ESBL activity.[5] Of these, 60.5% were nosocomial and 39.5% were community-acquired. The percentage of *E. coli* isolates with such resistance has fluctuated widely from a low of about 4% in 2002 to a high of 11% in 2007; this was estimated at about 6% in 2010. Subsequent SMART surveillance study in Spain from 2011 to 2015 analysed 5,343 isolates from IAI recovered in 11 centres. The reported prevalence rates of nosocomial infections and community-acquired infections were 53.7% and 46.3%, respectively.[219]

In Europe, the highest incidence of KPC-producing Carbapenemase-producing *Enterobacteriaceae* (CPE) was found in Mediterranean countries, especially Italy and Greece. While other carbapenemases might be present in Italy and Greece, KPC was found to be the most common aetiology of carbapenem resistance.[220]

Prevalence:

Since 2000, dramatic shifts in both the prevalence and types of antimicrobial resistance have been reported in Europe. Overall, the most concerning trends in Europe in 2013 were due to the growing incidence of resistance in Gram-negative bacteria such as *E. coli, Klebsiella pneumoniae, P. aeruginosa,* and *A. baumannii*.[221]

Regarding *E. coli and K. pneumoniae*, constant increases in antibiotic resistance have been noted, especially for third generation cephalosporins and carbapenems. Despite the best efforts of infectious disease experts to eradicate ESBL-producing *Enterobacteriaceae*, they are now endemic in Europe. During the years 2010 to 2013, resistance increased significantly in that third generation cephalosporins rose in *E. coli* (9.5% to 12.6%) and *K. pneumoniae* (22.8% to 30.0%). The majority of these were confirmed to be ESBL positive.[221] A consistent increasing trend in antimicrobial resistance to third generation of cephalosporin was found over the time period of six years (from 2013 to 2019) (*E. Coli* isolates from 12.6% to 15%, *Klebsiella spp*. isolates from 30% to 38%). The report also mentioned about 37% of *Enterobacter spp*. isolates. Carbapenem resistance was reported in 17% of *Klebsiella spp*. isolates, 26% of *P. aeruginosa* isolates, and 82% of *Acinetobacter baumannii* isolates as per the ECDC report in May 2023.[222]

More recently, the problem of resistance has focused on carbapenemases in *Enterobacteriaceae* (Carbapenemase-Producing *Enterobacteriaceae* [CPE]), most notably *K. pneumoniae* Carbapenemase (KPC) and OXA-48.[223] The importance of increasing carbapenem resistance in Europe has been emphasised by the European Centre for Disease Prevention And Control Working Group, EUSCAPE, targeting CPE.[224] Carbapenem resistance in *E. coli* remains uncommon, with resistance percentages of <0.1% reported by the majority of countries. Increasing resistance is mainly seen in the countries situated in southern and southeastern Europe.[225] In 2013, the mean carbapenem resistance in Europe for *K. pneumoniae* was 8.3% (59.4% in Greece) compared with 4.6% in 2010.[221, 224] Similarly, mean carbapenem resistance for *K. pneumoniae* reported in the EU/EEA region was 11.7% in 2021 compared with 7.1% in 2017.[226] Furthermore, combined resistance (MDR) to third-generation cephalosporins, fluoroquinolones, and aminoglycosides in *K. pneumoniae* was

20.9% in 2013 compared with 15.1% in 2010.[221] It was 21.2% in 2021 compared with 20.5% in 2017.[226]

The mean percentage of carbapenem resistance in *P. aeruginosa* was 18.1% in 2021 and 17.6% in 2013, which has remained relatively constant since 2010.

An analysis of 18,142 invasive clinical *Acinetobacter spp*. isolates from 30 European Countries in 2013-2017 via the European Antimicrobial Resistance Surveillance Network (EARS-Net) identified population-weighted mean proportion of carbapenem-non-susceptible *Acinetobacter spp*. (CNA) of 35.6% (95% CI: 29.7% - 42.0%).[227]

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

Age, gender, and race/ethnicity

From a single site in Germany, all inpatients colonised or infected with MRGN bacteria were prospectively identified by clinical microbiology. In 2002 to 2004, most of the members of this population were male (337/503 or 67.0%), and the median age was 55 years with a range of 0 to 89 years.[217]

In a multicentre, international, Phase 3 study, cases that involved hospitalised patients with Gram-negative resistant serious infection included 57 complicated skin structure infections (50.9%), 23 NP cases (20.5%), 19 cIAI cases (17%), 12 bacteraemia cases (10.7%), and 1 community-acquired pneumonia case (0.9%). Mean age was 55.4 years (SD 15.89 years); 61.6% of the patients were male, and 73.2% were White.[228]

In the SMART study referred to above, the frequency of infections that involved *Enterobacteriaceae* with ESBL activity increased by age category from 4.4% of isolates in those younger than 30 years of age, 5.9% in those 31 to 60 years of age, and 6.8% in those older than 60 years of age.[5]

A prior study indicates that total outpatient antibiotic consumption on a national scale is closely correlated to bacterial resistance development (Spearman coefficient $r=0.75$; $p<0.001$).[229, 230]

Risk factors

Risk factors including prolonged hospital stay, ICU stay, long-term care residency, and the hospital type and care level are associated with infection/colonisation.

Additionally, other factors driving antimicrobial resistance are increased antibiotic misuse or overuse in human and animal medicine, inadequate waste management or sewage disposal systems, food and medicine contamination, global mobility, and increased industrialisation.[231] Transmission/persistence risk factors include severe disease, decubitus ulcers, recent surgery, indwelling devices, delay in initiating antimicrobial therapy, and the selection pressure secondary to total antimicrobial use.[228, 229] The WHO's fact sheet on antimicrobial resistance enlisted poor infection and disease prevention and control in

healthcare facilities and farms, poor access to quality, affordable medicines, vaccines and diagnostics, and lack of awareness and knowledge or enforcement of legislation as key drivers for antimicrobial resistance.[232]

In a multivariate analysis of 924 Gram-negative infection episodes in a surveillance review, factors that independently predicted the development of resistant Gram-negative infections included, nosocomial infection (OR: 2.92; 95% CI: 1.44-5.93), infections related to haemodialysis dependency (OR: 1.93; 95% CI: 1.15-3.27), corticosteroid use (OR: 1.71; 95% CI: 1.07-2.72), and diabetes mellitus (OR: 1.72; 95% CI: 1.01-2.94).[233] Finally, carbapenems (e.g., meropenem, doripenem) are often considered reserved treatments for Gram-negative infections due to ESBL-producing organisms such as *P. aeruginosa* or *Enterobacteriaceae* (e.g., *K pneumoniae*).

However, with an increasing trend in carbapenemases producing organisms, resistance to carbapenems and β-lactam antibiotics is a risk factor for infections with limited treatment options.[234-236]

The main existing treatment options:

In general, carbapenems are the gold standard for treatment of ESBL-producing bacteria. However, in recent years, increasing rates of carbapenem resistance have been reported, thus, the need for carbapenem-sparing options exists.

In general, two old antimicrobials, including fosfomycin (discovered in 1969) and colistin (discovered in 1949), and a relatively newer agent, tigecycline, are considered as a last resort in managing MDR- and carbapenem-resistant Gram-negative infections. The Gram-negative spectrum of tigecycline includes ESBL-producing *Enterobacteriaceae*, KPC- and VIM-producing *K pneumoniae*, and *S maltophilia* strains. Similarly, colistin is active against *E. coli*, *Klebsiella* several species (spp.), *Enterobacter* spp., MDR *P. aeruginosa*, and *Acinetobacter* spp. However, lack of dosing guidance and renal toxicity limit the use of colistin.[237] Finally, fosfomycin, an antimetabolite inhibitor that has broader coverage and is active against both Gram-positive and Gram-negative MDRO and ESBL-producing *Enterobacteriaceae*, has been used in recent years.[234, 238, 239]

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

<u>Mortality</u>

Failure to eradicate a resistant Gram-negative infection within 7 days independently predicts 30 day mortality.[213] Excess risk may not be due to virulence per se but due to the delay in effective treatment and the limitations of subsequent therapies to rescue the patient from the infection.

A multivariate analysis involving 119,699 patients admitted to 537 ICUs in 10 European countries was conducted to assess the risk of death amongst patients with infections due to resistant organisms. Amongst patients with NP with resistant organisms, the risk of death was higher compared with patients with non-resistant infections (hazard ratio 1.2; 95% CI:

1.1-1.4). However, the risk of death did not differ amongst patients with BSIs due to resistant organisms compared with patients with infection due to antibiotic sensitive microorganisms (hazard ratio: 1.2; 95% CI: 0.9-1.5).[240]

In the Raymond surveillance review referred to above, the presence of a resistant Gram-negative infection proved to be an independent predictor of mortality within the studied population (OR: 2.23; 95% CI: 1.35-3.67). Overall crude mortality was 27.1%.[233]

A study on multidrug-resistant infection-associated mortality in Greece reported an overall mortality rate of 50.3% for 157 episodes of MDR-GN BSI over 12-month period.[241]

In the patients treated with CAZ-AVI for serious Gram-Negative infections with limited treatment options, 30 days-mortality ranged from 0% to 63%, as reported by a systematic review on 73 publications comprising 1,926 patients treated with CAZ-AVI. The reported 30-days mortality in CAZ-AVI group was lower than that reported in comparator groups with demonstrated statistical significance.[209]

Morbidity

Harm due to a resistant Gram-negative infection will be compounded by severity of illness, associated co-morbidities, infection source and organism, and, finally, host physiologic/immunologic compromise.[233]

Exposure to antibiotic-resistant strains can lead to colonisation with no overt infection in the healthy and immunocompetent patient but may lead to a life-threatening infection in the elderly or those with co-morbidities.[213]

Colonised patients and staff harm only others as reservoirs and vehicles,[228, 229] but in vulnerable populations, single- and MDR bacteria have a significant impact on mortality, hospital stay, and associated costs.[242]

Important co-morbidities:

For the indication of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options, the important co-morbidities are diabetes and pulmonary disease.[233]

SI.4.2. Indication: Infections due to Aerobic Gram-Negative Organisms in Patients with Limited Treatment Options (Paediatric Population)

Epidemiologic data among a paediatric population for infections due to aerobic Gram-negative organisms with limited treatment options were conducted for various conditions such as bronchopulmonary infections in cystic fibrosis, bacterial meningitis, complicated skin and soft tissue infections, bone and joint infections, or peritonitis associated with dialysis in patient on continuous ambulatory peritoneal dialysis.

Incidence:
No epidemiologic data specifying incidence of infections due to aerobic Gram-negative organisms with limited treatment options were identified.

Overall, bacterial meningitis incidence decreased from 6.37 to 1.58 (per 100,000 population) between 1989–1993 and 2014–2019 (IRR, 0.25 [95% confidence interval CI: .23–.26]; $p < .001$), as reported in a Netherlands-based study analysing 17,393 episodes that contained 5,960 episodes in pre-school children.[243]

Prevalence:

With introduction of vaccines against *N. meningitidis*, rates in children for bacterial meningitis was 5.2 per 100,000 from 1989 to 2011.[244]

The prevalence of meningitidis carriage (the first step of disease transmission) ranged from 7.5% to 12.5% among children aged between 0-18 years, as reported by a multicountry, observational study on 1,267 Turkish children and adolescents.[245]

In the paediatric population, bacterial meningitis due to *N. meningitidis* ranged from 7.5% to 46.9% across different geographical areas.[244] In neonates, *E. coli* and *S. pneumoniae* were the most common bacterial meningitis-causing pathogens in Africa (weighted means of 17.7% and 20.4%, respectively.[244]

N. meningitidis was the most common in children aged 1 to 5 years in Europe (47.0%).[244]

A two-year French prospective cohort study enrolled 131 consecutive children who were admitted for osteoarticular infections (OAI) and 86 were bacteriologically documented cases of OAI. *K. kingae* was the leading cause of OAI in this paediatric series (45%), followed by *S.aureus* (29%).[246]

A large case series assessing *S.aureus* clinical, phenotypic and genotypic characteristics over a span of 8 years demonstrated that 44 of 123 (35.8%) children had MRSA-induced OAI.[247]

The frequency of *P. aeruginosa* bacteraemia in children with primary site infections that included the lung, skin and soft tissue, catheter-related, urinary tract, or ear have been reported in a South Korean observational study.[248]

This ten-year study with 62 paediatric patients, found that on average, 7.5 episodes of *P. aeruginosa* bacteraemia occurred in one year with a range of 1-15 cases per year. The mean incidence rate was 0.09 episodes per 1,000 patient-admission days per year.[249]

A US population-based study examined the incidence rate and site of infection for acquiring gram-negative bloodstream infection in children (n=56). Underlying conditions for these children included urologic disorders such as kidney stones, end-stage renal disease, and cystic fibrosis.[250]

Among monomicrobial gram-negative bloodstream isolates, *Escherichia coli* was the most common microorganism (38%), followed by *Pseudomonas aeruginosa* (13%), Klebsiella

spp. (9%), Enterobacter spp. (6%), Salmonella spp. (6%), Acinetobacter spp. (6%), Haemophilus spp. (4%), and others (17%).[250]

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

Age, gender, and race/ethnicity

It is estimated that the peak incidence of bacterial meningitis occurs in children younger than 2 months of age and that at least 75% of cases occur in those younger than 5 years of age.[251] In a Finland observational study (1995 to 2014), the age stratified incidence rates of bacterial meningitis showed that children <2 years of age accounted for 20% of cases (268 out of 1,361) with an incidence rate of 11.38 cases per 100,000 person-years.[252] In children 2 to 4 years of age, 70 cases (5%) of bacterial meningitis were reported during 1995 to 2014 (1.94 cases per 100,000 person-years).[252] The most common pathogens in this age group were *N. meningitidis* (1.33 cases per 100,000 person-years).[252]

In a UK-based trend analysis, the prevalence of laboratory-confirmed bacterial meningitis between 2012-2019, was 7.8% (319 of 4,073) in infants aged 3–11 months, which decreased till the age of 14 years (6.1% in 1–4-year-olds (249 of 4,073) and 3.6% in 5–14 year-olds (146 of 4,073). Infants aged <3 months had the highest mean incidence (55.6 per 100,000; 95% CI, 47.7–63.5) followed by 3–11-month-olds (8.1 per 100,000; 95% CI: 7.1–9.0).[253]

The incidence rate of 0.80 cases per 100,000 person-years. *N. meningitidis* and *S. pneumoniae* were the main causes (0.52 and 0.20 cases per 100,000 person-years, respectively).[252]

Among the 86 bacteriologically documented cases of OAI in a French study, the distribution of *Kingella kingae* infections by age groups were as follows: 0% for those < 6 months of age; 70% for those 6 months to < 1 year of age; 78.1% for those 1 to 2 years of age; 54.5% for those over 2 to 6 years of age; 6.3% for those over 6 years to 12 years; and 0% for those >12 years of age.[246]

Risk factors

Risk factors vary by diseases in this paediatric population. Although poor living conditions increase the risk of meningitis, other factors, such as crowded attendance in day-care facilities, contribute to the frequency of disease.[254] For complicated soft skin and tissue infections, risk factors include day-care attendance, and outbreak settings such as newborn nurseries.[255]

The main existing treatment options:

As for adults, carbapenems are generally considered the treatment of choice for infections due to ESBL-producing bacteria in children. For Gram-negative infections that are resistant to carbapenems, available treatment options that are approved for use in children remain limited; treatment regimens that are typically employed are generally similar to those utilized in adults. Tigecycline, which has activity against ESBL-producing *Enterobacteriaceae*, KPC-

and VIM-producing *K pneumoniae*, and *S maltophilia* strains, may be used in children 8 years of age or older but is not indicated in children <8 years of age due to the lack of safety and efficacy data in this age group and because it may result in permanent teeth discolouration.[256] Older drugs, such as colistin, polymyxin B and fosfomycin are also utilized in children with infections due MDR pathogens. These agents are typically used in combination with other antibiotics, dependent on the specific pathogen. For example, colistin may be combined with aztreonam, meropenem, fosfomycin, or rifampicin for treatment of VIM and NDM *K. pneumoniae* infections. For carbapenem resistant *K. pneumoniae* and/or other carbapenem-resistant *Enterobacteriaceae* infections, tigecycline may be combined with rifampin, fosfomycin or colistin.[257]

The problematic overuse and misuse of antibiotics (for wrong diagnoses and indications, or at wrong dosage) and the lack of paediatric-specific data and trials calls for a cautious decision. The partly age-dependent changes of a developing system of cytochromes determine a rather diverse population in terms of biochemical characteristics and pharmacokinetics profiles, hard to easily codify in an age- or weight-dependent dosage. The paediatric population is also penalized by the contraindications of tetracyclines and fluoroquinolones, and by congenital malformations which often require repeated hospitalisations and pharmacological and surgical treatments from a very young age. Emerging threats for the paediatric age are MRSA, vancomycin resistant *Staphylococcus aureus* (VRSA), ESBL-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae and the alarming colistin resistance.

Over the last few years, several new antibiotics effective against Carbapenem-resistant organism (CRO) have been approved. Some of them (e.g., plazomicin, imipenem-cilastatin-relebactam or cefiderocol) are currently approved for use only by adults; others (e.g., CAZ-AVI) have recently been approved for use by children.[258]

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

Mortality

Ranges in mortality exist between the different conditions with infections caused by aerobic gram-negative bacteria in the paediatric population. For example, 21.3% (n=19) of cases with bacterial meningitis died in a cohort of 89 French paediatric patients.[259]

Mortality rates in children with CRO infections range from 8% to 52%.[258]

The median age of diagnosis for bacterial meningitis who died was 7 months.[259] A total of 19 deaths occurred within 48 hours of hospital admission and all of them were attributed to bacterial meningitis. Two of the children who died had significant comorbidities (one child had sickle cell disease, and another had chronic renal insufficiency).[259]

A South Korean retrospective cohort study of 62 paediatric patients reported an overall case fatality associated with P. aeruginosa bacteraemia of 14.5% (9 of 62).[249] The fatality rate of the multidrug resistance *P. aeruginosa* group was 57.1% compared with 9.1% in the non-MDR group.[249]

Morbidity

The risk of prolonged morbidity and long-term sequelae exists for any of the conditions with infections caused by aerobic gram-negative bacteria. The morbidity for bacterial meningitis and OAI is listed. Paediatric bacterial meningitis is a severe, life-threatening infection of the membranes (meninges) surrounding the brain and spinal cord. The infection may be associated with long-term, potentially devastating sequelae even when it is aggressively managed.[251] Systemic complications in children include septic shock, disseminated intravascular coagulation, acute respiratory distress syndrome, and septic or reactive arthritis. Even with treatment, there are significant long-term neurologic effects.[251] Neurologic sequelae include sensorineural hearing loss, seizures, motor problems, hydrocephalus, and many other cognitive and behavioural problems.[251]

Children with OAI may experience substantial long-term morbidity including chronic infection, pathologic fracture, angular deformity, and growth arrest.[260]

Important co-morbidities:

Important comorbid conditions among children with infections due to aerobic Gram-negative organisms in patients with limited treatment options can include haematological or oncological disease, cardiovascular disease, nephrological or urological disease, neurological disease, hepatobiliary disease or congenital immune deficiency.[249]

SI.4.3. Indication: Infections due to Aerobic Gram-Negative Organisms in Patients with Limited Treatment Options (Neonatal Population)

Incidence:

Globally, the number of incident cases of neonatal sepsis and other neonatal infections grew by 12.8% per year (5.59 million in 1990 to 6.31 million in 2019), and the number of deaths dropped by 12.9% per year as reported in 2019 global disease burden study including 204 countries.[261] Overall age standardized annual incidence rate (ASIR) increased from 85.21 to 97.43 per 100,000 live births in two decades. In Europe, the ASIR per 100,000 live births was 56.35 in Central Europe, 130.81 in Eastern Europe, and 16.21 in Western Europe. Compared to the ASIR in high-income sociodemographic index (SDI) regions (28.54 per 100,000 live births), ASIRs were higher in low, low-middle, middle and middle high SDI regions in 2019 (90.12 to 115.57 per 100,000 live births).[261]

A global systematic review that included 152 studies from 54 countries on neonatal infections found that Gram-negative pathogens accounted for 53% of neonatal bacteraemia in low/middle-income (LMIC) countries and 28% in high-income countries (HIC).[262] Similarly, a study on neonates with nosocomial sepsis in Turkey between January 2003 and September 2016 estimated that gram-negative pathogens accounted for 27.1% of (251 of 925 positive blood culture samples) of neonatal sepsis.[263] In the aforementioned global systematic review, the overall incidence of neonatal Gram-negative bacteraemia was 2.01 (95% CI, 1.15-3.51) per 1,000 live births.[262] It was also noted that the incidence of neonatal Gram-negative bacteraemia in LMIC was 5 times higher than HIC (0.73 vs 4.35 per 1,000 live births).[262]

The incidence of early onset (0-6 days after birth) sepsis caused by Gram-negative pathogens was 0.25 per 1,000 live births in a retrospective study on 558 positive cultures from neonates from 1997-2017 in western Sweden.[264] Another retrospective cohort study in Sweden found a cumulative incidence of 0.35 per 1,000 live births during 2006-2016 for sepsis caused by Gram-negative pathogens.[265]

Escherichia coli is the leading Gram-negative pathogen in HIC, followed by *Klebsiella spp*.[262] The annual incidence of neonatal sepsis caused by *Escherichia coli* significantly increased from 4.8 to 8.5 per 1,000 live births (LB) (OR: 2.0 [IQR: 1.1–3.9] $p < 0.05$) in very low birth weight neonates (birth weight ≤1,500 g) in an analysis of neonates diagnosed with sepsis between 1996 and 2018 from 44 neonatal units in Spain.[266] In the US, the incidence of early onset neonatal sepsis due to *Escherichia coli* was 4.3 per 1,000 live births, as reported by a retrospective cohort study in California from 2010-2017 at 136 NICUs.[267]

Prevalence:

In a 20-year retrospective study, gram-negative bacteria accounted for 27.4% (1,933 of 7,036) of nosocomial sepsis episodes in very low birth weight infants registered in Grupo Castrillo neonatal network in Spain. The most common pathogen identified was *Klebsiella spp.* (35% (683 of 1,933 Gram negative pathogens).[266]

In LMIC, the pooled prevalence of neonatal Carbapenem-resistant K. Pneumoniae infection was 0.3% (95% CI: 0.2% -0.3%) according to a systematic review containing 23 studies with reported data on neonatal CRKP from 11 LMIC countries on 123,842 hospitalized neonates' data.[268] Another systematic review comprising of 88 studies from 19 low and LMICs (LLMICs) that contained data of 10,458 Gram-negative neonatal sepsis isolates reported the pooled prevalence of 60% of Gram-negative sepsis (95% CI: 55% - 65%).[269] This appears to be similar to the infant bacteraemia prevalence range reported in a systematic review from 90 LMIC studies (49% to 57%).[262]

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

Age, gender, and race/ethnicity

A study on bacterial meningitis cases reported the age distribution of bacterial meningitis cases included 20.0% (732 of 4073) in <3 months. Infants aged <3 months had the highest mean incidence (55.6 cases per 100,000 persons; 95% CI, 47.7–63.5) followed by 3–11-month-olds (8.1 per 100,000 persons; 95% CI: 7.1 – 9.0).[253]

The 2019 Global Burden of Disease study estimated that the age-standardized incidence of neonatal sepsis and other neonatal infections in males, 99.74 per 100,000 live births, was slightly higher than that in females, 94.96 per 100,000 live births, in 2019.[261]

The Spanish retrospective study between 1996-2016 reported that the median postnatal age of sepsis onset was 13 days (1QR: 9-23 days). Male neonates with very low birth weight (VLBW) were more prone to nosocomial sepsis compared to females (55% [3,870 of 7,036

sepsis episodes]).[266] However, an epidemiological retrospective study in Sweden reported no gender differences in proportions of early onset neonatal infections.[264]

Risk factors

The risk factors for Gram-negative neonatal sepsis/bacteraemia can be of two types: 1. Patient-level and 2. Centre-level. Several common risk factors identified in patients include maternal prenatal antibiotic exposure, prolonged hospitalization, prolonged rupture of membranes in pregnancy, pre-term birth, VLBW, respiratory distress, physical proximity to another patient with MDR-GN colonization or infection, maternal and neonatal MDR-GN colonization, underlying renal disease, neutropenia/leukopaenia/cytopaenia. At center-level, poor infection control practices and lack of pesticides control, contamination in expressed breast milk like factors may cause risk of worsening of neonatal infections.[270-273]

A systematic review reported several additional perinatal risk factors that may lead to early onset neonatal sepsis including perinatal asphyxia or intrauterine distress, meconium contamination in amniotic fluid, chorioamnionitis, premature rupture of membranes, maternal UTI or reproductive tract infection, perinatal fever and vaginal examinational ≥ 3 times.[274]

The main existing treatment options

The emergence of MDR-GN bacteria-induced antimicrobial resistance in neonates is a serious concern due to their vulnerabile condition. β-lactam/β-lactamase inhibitors (CAZ-AVI, ceftolozane-tazobactam, imipenem/cilastatin–relabactam, and meropenem–vaborbactam) and a siderophore cephalosporin (cefiderocol) were the novel agents reported for the treatment of GN infections in neonates. Several repurposed antimicrobial agents for treatment include colistin, tigecyclin, and fosfomycin.

Nowades, colistin has been used as the last resort because of its known neurotoxicity and nephrotoxicity. The CRE infections could be treated using the combination of colistin an meropenem, amikacin, or ciprofloxacin, or high-dose meropenem and CAZ-AVI. The scarcity of safety and efficacy/effectiveness data, resulting from limited numbers of clinical trials on new antibiotics, precludes their inclusion as therapeuthic options for neonates. Also, the limited information and guidance on dosing and the extent of off-label use of old antibiotics in neonates warrant further research.[275, 276]

A case report and literature review proved that the off-label treatment against resistant *K. pneumoniae* with CAZ-AVI for 17 days was safe and effective in a one-month-old patient. A year later, the patient was healthy and had normal cognitive development.[277]

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

Mortality

The pooled in-hospital mortality due to neonatal Carbapenem-resistant K. Pneumoniae (CRKP) infection was 0.3% (95% CI: 0.2% -0.3%) according to a systematic review

containing 21 studies with reported data on neonatal CRKP infections and 79 neonatal deaths from 123,842 hospitalized neonates' data.[268] The highest decline was reported in death cases (-78.02%) and age-standardised mortality rate (-65.85%) from 1990-2019 in Central Europe. In contrast, Westen and Eastern Sub-Saharan Africa reported 63,840 and 46,260 neonatal sepsis deaths. When combined with South Asian neonatal sepsis death counts, it accounted for almost 75% of global NS deaths.[261]

A 20-year retrospective study in Spain reported a decline from 10.0% to 7.3% in mortality attributed to gram-negative bacteria during study period (18.5%).[266] Another retrospective study in western Sweden reported the rate of aerobic Gram-negative bacteria-related case fatality rate in neonates during 1997-2017 of 13% (6 deaths of 47 cases of GNB infections).[264] The neonates with late onset sepsis presented 2.2 and 4.8 times higher odds (crude odds ratio) of dying before discharge at NICU (5 days case fatality) than GNB-sepsis group and suspected sepsis group, respectively as per a 10-year, retrospective matched cohort study in Stockholm.[265]

In neonatal sepsis-causing bacterial pathogens, in both phases – early and late-onset sepsis, the most common pathogens that caused sepsis-related death were *K. pneumoniae* (18.2%) and *Pseudomonas aeruginosa* (13.6%), as reported in a 20-year medical records-based study in South Korea.[278]

According to a health records-based trend analysis from 2012-2019 in the UK on 6,554 laboratory-confirmed cases of Neisseria meningitidis or Streptococcus pneumoniae, the case fatality rate for bacterial meningitis was 9.3% (111 of 1,198) in infants aged <3-month.[253] Overall in-hospital mortality rate was 2.77% (15 neonatal deaths out of 541 enrolled neonates for various surgical pathologies).[279]

Morbidity

Neurological complications may occur after neonatal bacteraemia. This may include seizures, hydrocephalus, encephalomalacia, cerebral infarction, subdural empyema, ventriculitis, abscess, NEC.[280, 281]

Important co-morbidities

Important comorbidities in Gram-negative neonatal sepsis included, intraventricular haemorrhage, persistent pulmonary hypertension of newborn, bronchopulmonary dysplasia, retinopathy of prematurity, disseminated intravascular coagulation.[282]

Module SII. Non-Clinical Part of the Safety Specification

Avibactam (AVI) has been shown to be well tolerated in nonclinical species and is not associated with target organ toxicity in adult animals with the exception of local tolerance issues when administered IV via a peripheral vein.

A summary of non-clinical safety concerns that are not adequately addressed by clinical data or of unknown significance, along with projected relevance to humans, are listed in Table 16.

Table 16. Key Safety Findings and Relevance to Human Usage

Findings (from Non-clinical Studies)	Relevance to Human Usage
Toxicity **Reproductive and developmental toxicity – pregnancy** Reproduction studies have been performed with CAZ in mice and rats at doses up to 40 times the human dose and have revealed no evidence of impaired fertility or harm to the foetus.[172,283] In a male rat fertility study, there was no effect of AVI treatment on gonadal function, mating behaviour, or fertility. In a female rat fertility study, there was no effect of AVI treatment on mating behaviour or fertility, although a dose-related effect on early pregnancy was observed (slight increase in pre- and post-implantation loss with a resulting decrease in live litter size at doses of 500 mg/kg/day and above). Following administration of AVI throughout pregnancy and lactation in rats at maternal exposures greater than or equal to approximately 1.5 times the human therapeutic exposures, there was dilatation of the kidney and ureters in the rat pups. In pregnant rabbits at exposures of AVI approximately 8-fold higher than those observed in humans at 500 mg 3 times daily, there was a slight effect on foetal weight and slight retardation of ossification of a few bones in the foetus.	**Unknown** As a class, cephalosporins have not been studied extensively in pregnancy. Pregnant women were excluded from clinical studies.
Lactation – breast-feeding exposure CAZ-AVI is excreted in breast milk in rats. AVI was detected in the milk and pups of nursing rats demonstrating that AVI can be excreted in breast milk. However, exposure in the 7-day old suckling pups was minimal compared with plasma of the dams.	**Unknown** Lactating women were excluded from clinical studies.
Juvenile Toxicity	**Potentially relevant** The risk of nephrotoxicity in humans is low with CAZ-AVI. However, the ceftazidime SmPC Section 4.4 warns[284] against concurrent use with nephrotoxic medications such as potent diuretics (e.g., furosemide) and aminoglycosides. Elimination of CAZ and AVI is decreased in patients with moderate or severe renal impairment and end-stage renal disease,

Table 16. Key Safety Findings and Relevance to Human Usage

Findings (from Non-clinical Studies)	Relevance to Human Usage
CAZ-AVI was dosed via an IV bolus injection into the tail vein of suckling rats once daily for 14 days from post-natal Day (PND) 7 to PND. Renal cortical cysts were observed at necropsy and by histology and were still present at the end of the 5-week recovery phase. Rare foci of cortical peri-tubular fibrosis were noted in both control and treated rats at PND56. The cysts covered a small proportion of the cortex and did not appear to have any significant implications for the animals (no adverse clinical signs, no effects on body weight gain and no significant changes in clinical pathology or organ weights) and therefore were considered to be non-adverse.	including patients undergoing haemodialysis; the CAZ-AVI dose should be reduced in patients with creatinine clearance ≤50 mL/min.
Renal toxicity In repeat-dose toxicity studies in the rat, CAZ was associated with increased kidney weight. Renal toxicity was observed at very high doses (>8 g/kg/day). No toxicity was identified in dogs with CAZ at doses of up to 540 mg/kg/day.[285] There was no consistent pattern of renal findings when AVI was dosed to adult animals and no renal findings when CAZ-AVI was dosed to rats and dogs.	**Potentially relevant** Refer to above.
Bacterial resistance development CAZ-AVI is not active against metallo β lactamase-producing bacteria. Organisms that express these enzymes and are therefore resistant to CAZ-AVI occur at very variable rates between countries and between healthcare facilities within countries. Resistance to CAZ-AVI could be selected in *temoniera,* Cefotaximases (CTX-M), and *Klebsiella pneumoniae* carbapenemase β-lactamase-producing strains in vitro at frequencies of 10^7 to 10^9. In some mutants, the β-lactamase sequence had changed; in others, the change appeared to be associated with altered permeability, on the basis of increases in minimum inhibitory concentrations of unrelated antibiotics. Resistance may also be mediated by bacterial impermeability or drug efflux pump mechanisms. One (1) or more of these mechanisms may co-exist in a single bacterial isolate.	**Potentially relevant** In vitro data indicated that CAZ-AVI is not active against the following species: *Enterococcus faecalis, Enterococcus faecium, and S. aureus* (ie., Methicillin-Resistant *Staphylococcus Aureus*). In vitro resistance studies showed that the frequency of spontaneous resistance to CAZ-AVI was low across the *Enterobacteriaceae* and *P. aeruginosa* strains tested. The Important Potential Risk of Bacterial resistance development is proposed to be reclassified as a potential risk, not considered important for inclusion in the list of the Safety concerns in the RMP.

Table 16. Key Safety Findings and Relevance to Human Usage

Findings (from Non-clinical Studies)	Relevance to Human Usage
Infusion site reactions (local tolerance) Poor local tolerance at the infusion site was observed when AVI (≥500 mg/kg/day) was dosed via a peripheral vein in rats. In the 4-week rat study, the severity of the findings resulted in the early termination at the highest dose tested (1200 mg/kg/day). Minimal irritant effects were also observed at the infusion site in the 4-week dog study. However, when AVI was administered via a central vein, infusion site reactions were not observed. Intravenous infusion of CAZ in rats via a peripheral vein also resulted in poor local tolerance at the infusion site. The severity of these findings appeared to be increased with the combination of CAZ and AVI in the 4-week rat study.	**Potentially relevant** In clinical studies, infusion site reactions occurred with low frequency and were generally mild; there have been no reports of severe reactions or patient discontinuations due to infusion site tolerability in the clinical studies completed to date.

AVI = Avibactam; CAZ = Ceftazidime; CAZ-AVI = Ceftazidime-Avibactam; SmPC = Summary of Product Characteristics.

Module SIII. Clinical Trial Exposure

Co-development of CAZ-AVI

The development of CAZ-AVI was initially undertaken by Novexel, which was acquired by Astra Zeneca in March 2010, at which point AZ and Cerexa Inc. (a wholly owned subsidiary of Forest Laboratories) entered into a collaborative agreement to co-develop and commercialise CAZ-AVI. In December 2016, Pfizer acquired the development, regulatory approval, and commercialisation rights for CAZ-AVI in the EU and other markets outside of North America. A paediatric development programme is being undertaken to evaluate the use of CAZ-AVI in paediatric patients (Paediatric Investigation Plan (PIP) number European Medicines Agency (EMEA-001313-PIP01-12). To date, 2 clinical studies of CAZ-AVI have been completed in patients ≥3 months old with cIAI or cUTI. There are no clinical data in paediatric subject for HAP.

CAZ-AVI is being developed by Pfizer and AbbVie (formerly Allergan Sales, LLC), for the treatment of patients with infections caused by Gram-negative pathogens, including pathogens that are resistant to ceftazidime.

Clinical Study Information

Details of the individual studies, pertinent to the RMP are provided in Annex 2.

Global Access Programme

Since 01 February 2015, a compassionate use global access programme (GAP) for individual named patient requests for CAZ-AVI has been in place for EU countries and other countries

outside of the US and Canada. This was managed by Clingen, a UK based company specialised in running global access programmes. Cumulatively, CAZ-AVI has been supplied through the GAP to 1048 individual named patients (of which 200 received more than one treatment course) from the following countries: Australia 21, Bahrain 2, Belgium 35; Chile 16, Costa Rica 1, France 32, Greece 6, Hong Kong 12, India 4, Ireland 13, Israel 5, Italy 401, Kuwait 1, Lebanon 3, Malaysia 1 Malta 1, Netherlands 1, New Zealand 1, Poland 7, Portugal 4, Saudi Arabia 6, Singapore 129, Slovenia 5, Spain 310, Switzerland 11, Tunisia 1, Turkey 2 , and United Kingdom 16. The GAP program was officially closed on 30 November 2020. The last patient receiving the product was in March 2020 and no initial or follow up AEs from the GAP programme were reported since its closure.

Overall, there is no relevant information pertaining to other therapeutic uses of CAZ-AVI for this reporting period and no new safety issues have been identified from the GAP programme.

Clinical trial exposure

The CAZ-AVI clinical development programme consists of 12 Phase 1 clinical studies (in healthy volunteers, elderly subjects, and subjects with various degrees of renal impairment), two phase 2 studies in patients with cIAI (1 for adult and 1 paediatric patients (aged ≥3 months to <18 years)), two phase 2 studies in patients with cUTI (1 for adult and 1 paediatric patients (aged ≥3 months to <18 years)), and 5 adult phase 3 studies in patients with cIAI, cUTI and NP. Ongoing studies are not within the scope of this presentation.
Of the 12 Phase 1 studies, 3 studies (D4280C00008, NXL104/1003, and NXL104/1004) are not included in the RMP analyses because the subjects enrolled in these studies were exposed to AVI alone and not CAZ-AVI.
The remaining 9 Phase 1 studies are within the scope of this document and include: NXL104/1001 (C3591009), NXL104/1002 (C3591010), D4280C00007 (C3591017), D4280C00009 (C3591019), D4280C00010 (C3591020), D4280C00011 (C3591021), D4280C00012 (C3591022), D4280C00020 (C3591007), and D4280C00023 (C3591023).

Two (2) double-blind, Phase 2 studies (NXL104/2001 and NXL104/2002) were conducted in adult patients with cUTI and cIAI, respectively.

Two (2) single-blind, Phase 2 studies (C3591004 and C3591005) were conducted in paediatric patients with cIAI and cUTI, respectively.

Four (4) double-blind, Phase 3 studies (RECLAIM, RECLAIM3, RECAPTURE and REPROVE) and 1 open-label, Phase 3 study (REPRISE) conducted in patients with cIAI (RECLAIM, RECLAIM3 and REPRISE-cIAI) or cUTI (RECAPTURE and REPRISE-cUTI), or NP (REPROVE).

The cIAI data consist of data from RECLAIM (a Phase 3, double-blind study conducted under identical protocols D4280C00001(C3591015) and D4280C00005 (C3591008) that were merged into a single inferential database), RECLAIM3 (a Phase 3, double-blind study), Study 2002 (a Phase 2 double-blind study), and REPRISE-cIAI (a Phase 3, open-label study). RECLAIM, RECLAIM3, and Study 2002 evaluated patients 18 years of age or older and

included a CAZ-AVI dose of 2000 mg CAZ + 500 mg AVI and Metronidazole (MTZ) 500 mg every 8 hours (q8h). The active comparator was meropenem 1 g q8h for these 2 studies. REPRISE-cIAI evaluated patients 18 years of age or older with a CAZ-AVI dose of 2000 mg CAZ + 500 mg AVI and MTZ 500 mg q8h with the Best Available Therapy (BAT) as the comparator.

The cUTI data consist of data from RECAPTURE (a Phase 3, double-blind study conducted under identical protocols D4280C00002 (C3591001) and D4280C00004 (C3591002) that were merged into a single inferential database), Study 2001 (a Phase 2, double-blind study), and REPRISE-cUTI (a Phase 3, open-label study). These studies evaluated patients 18 years of age or older and included a CAZ-AVI dose of 500 mg CAZ + 125 mg AVI q8h compared with imipenem-cilastatin 500 mg q6h as the active comparator (Study 2001) and a CAZ-AVI dose of 2000 mg CAZ + 500 mg AVI q8h compared with BAT as the active comparator (REPRISE-cUTI) or doripenem as the active comparator (RECAPTURE).

The HAP data consist of data from REPROVE (a Phase 3, randomised, double-blind, parallel-group comparative study of CAZ-AVI versus meropenem in the treatment of NP, including VAP in hospitalised adults). This study evaluated patients 18 years of age or older and included a CAZ-AVI dose of 2000 mg ceftazidime + 500 mg avibactam compared with meropenem 1000 mg as the active comparator.

Two further paediatric studies (C3591024 and C3591025) were completed subsequently. C3591025 was a Phase 1 study in 3 months to <18-year-old children with NP, and C3591024 was Phase 2a study in neonates and infants aged <3 months with suspected or confirmed infections due to Gram-negative pathogens (C3591024).

Aim of study C3591025 was to characterize the PK of CAZ-AVI and assess its safety and tolerability following a single IV infusion in hospitalized paediatric participants (age ≥3 months to <18 years at screening) with suspected or confirmed NP. Due to approval of the HAP/VAP indication in paediatric patients in the EU in October 2020 (ahead of completion of this study) as well as due to slow enrolment, the MAH decided to terminate this study early. At the time of study termination only 4 participants had been enrolled. The decision for termination was not taken for any safety reasons. No data from this study have been submitted to any HA in support of any indications. Due to the low enrolment providing data per cohort would risk re-identification of participants. Therefore, no data regarding this study are included in this RMP.

Study C3592024 was an open-label, non-randomized multi-center study and conducted to evaluate the PK, safety, tolerability, and descriptive efficacy of a single (Part A) and multiple doses (Part B) of CAZ-AVI in infants and premature neonates (newborns <3 months of age down to a gestational age of 26 weeks) with suspected or confirmed infections due to Gram-negative pathogens requiring IV antibiotic treatment.

Clinical trial exposure pertinent to adult population

A total of 16 studies involving adults are included in the exposure and risk table data pools; 9 Phase 1 studies, 2 Phase 2 studies, and 5 Phase 3 studies (RECLAIM, RECLAIM3,

RECAPTURE, REPRISE and REPROVE). Adult data pooling for the exposure tables is presented in Table 17.

Table 17. Data Pooling for Exposure – Adult population

Indication	Study Numbers
By indication; randomised, blinded study population	
cIAI[a]	NXL104/2002; D4280C00001 and D4280C00005 (RECLAIM); D4280C00018 (RECLAIM3)
cUTI	NXL104/2001; D4280C00002 and D4280C00004 (RECAPTURE)
HAP	D4281C00001 (REPROVE)
By indication; all clinical study populations	
cIAI[a]	NXL104/2002; D4280C00001 and D4280C00005 (RECLAIM); D4280C00006 (REPRISE-cIAI); D4280C00018 (RECLAIM3)
cUTI	NXL104/2001; D4280C00002 and D4280C00004 (RECAPTURE); D4280C00006 (REPRISE-cUTI)
HAP	D4281C00001 (REPROVE)
All indications; adult clinical study populations	
NXL104/1001; NXL104/1002; D4280C00007; D4280C00009; D4280C00010; D4280C00011; D4280C00012; D4280C00020; D4280C00023; NXL104/2001; NXL104/2002; D4280C00001 and D4280C00005 (RECLAIM); D4280C00002 and D4280C00004 (RECAPTURE); D4280C00006 (REPRISE); D4280C00018 (RECLAIM3); D4281C00001 (REPROVE)	

CAZ-AVI: Ceftazidime-avibactam; cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated Urinary Tract Infection; HAP= Hospital-acquired pneumonia.

a. Subjects with cIAI were treated with CAZ-AVI and metronidazole.

Clinical trial exposure pertinent to the paediatric indications of cIAI and cUTI in patients ≥3 months of age to <18 years; and study C3591024 (from birth to < 3 months of age)

Table 18. Data Pooling for Exposure – Paediatric Population (≥3 months to < 18 years)

Indication	Study Numbers
cIAI	C3591004[3] - ANDI
cUTI	C3591005[4] - KURA

[3] A single blind, randomised, multi-centre, active controlled, trial to evaluate safety, tolerability, pharmacokinetics and efficacy of CAZ-AVI when given in combination with metronidazole, compared with meropenem, in children from 3 months to less than 18 years of age

[4] A single blind, randomised, multi centre, active controlled trial to evaluate safety, tolerability, pharmacokinetics and efficacy of CAZ-AVI compared with cefepime in children from 3 months to less than 18 years of age

The paediatric data consist of data from ANDI and KURA, two Phase 2 single-blind, randomized, comparative clinical studies, in patients aged 3 months to <18 years with cIAI and cUTI, respectively. Patients treated with CAZ-AVI in ANDI also received metronidazole (administered per local label; suggested dose: 10 mg/kg every 8 hours, administered IV over 20 to 30 minutes). The active comparator was meropenem in ANDI and cefepime in KURA.

Study C3591024 (paediatrics from birth to < 3 months)

Due to the different study design and different indication in C3591024 from the already pooled paediatric studies KURA and ANDI (3 months to 17 years age), no data will be pooled between these age categories. Only in Table 23 the data will be jointly presented, all other exposure data for C3591024 will be presented separately.

The primary objective in each study (C3591004 and C3591005) was to assess safety and tolerability of ceftazidime-avibactam (+/- metronidazole). Secondary objectives included assessment of PK and efficacy; efficacy was a descriptive endpoint in both studies. Doses of CAZ-AVI were based on the age and weight with adjustment according to renal function (see Table 19).

Table 19. CAZ-AVI Dose Regimens by Age, Weight and Creatinine Clearance in studies C3591004 and C3591005

Cohort	Age range	Body weight	CAZ-AVI dose CrCl ≥50 mL/min	CAZ-AVI dose CrCl ≥30 to <50 mL/min
CAZ-AVI must be administered as a 50 to 100 mL infusion (dependent on dose) over 2 hours every 8 hours (±30 minutes)				
1	12 years to <18 years	≥40 kg	2000 mg CAZ / 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	12 years to <18 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
2	6 years to <12 years	≥40 kg	2000 mg CAZ/ 500 mg AVI	1000 mg CAZ/ 250 mg AVI
	6 years to <12 years	<40 kg	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
3	2 years to <6 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4a	1 year to <2 years	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	6 months to <1 year	All	50 mg/kg CAZ/ 12.5 mg/kg AVI	25 mg/kg CAZ/ 6.25 mg/kg AVI
4b	3 months to <6 months	All	40 mg/kg CAZ/ 10 mg/kg AVI	20 mg/kg CAZ/ 5 mg/kg AVI

Source: study synopsis C3591004

Table 20. CAZ-AVI Weight-based Dosing for Each Cohort in study C3591024 (from birth to < 3 months)

Cohort	Age	CAZ-AVI weight-based dose	Infusion		
			Volume	Duration	Frequency
1	>28 days[a] to <3 months old	30 mg/kg CAZ 7.5 mg/kg AVI	Varies, will not exceed 2 mL/kg/dose	120 min	q8h (Part B Only)
2	GA ≥37 weeks and ≤28 days old	20 mg/kg CAZ 5.0 mg/kg AVI			
3	GA ≥26 weeks to <37 weeks and ≤28 days old	20 mg/kg CAZ 5.0 mg/kg AVI			

a. Includes term infants (GA ≥37 weeks) >28 days of age and pre-term infants with corrected age >28 days. Corrected age = Subtract the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age was used only for determining eligibility of pre-term infants in Cohort 1. Actual age (chronological age) was used for determining eligibility of pre-term neonates in Cohort 3.
Source: CSR, Appendix 16.1.1, Protocol Table 2

Details of CAZ-AVI adult and paediatric exposure (≥3 months to <18 years) in the development programme are provided from Table 21 to Table 41. Exposure data for patients with limited treatment options are not presented in Table 21, Table 24, Table 28, Table 35 and Table 39 as no clinical data are available.

Table 21. Duration of Exposure to CAZ-AVI (by indication) - Adult Clinical Study Population (Safety Analysis Set)

Duration of exposure	Persons	Person time (Patient days)
cIAI (Studies NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00006 [REPRISE-cIAI]; D4280C00018 [RECLAIM3])		
1 day	16	16
2-4 days	38	115
5-10 days	634	4295
11-14 days	162	2065
15-21 days	5	96
>21 days	0	0
Total		6587
cUTI (Studies NXL104/2001; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE-cUTI])		
1 day	6	6
2-4 days	46	155
5-10 days	612	4703
11-14 days	53	669
15-21 days	14	265
>21 days	0	0
Total		5798
HAP (Study D4281C00001 [REPROVE])		
1 day	8	8
2-4 days	26	77
5-10 days	234	1894
11-14 days	168	2176
15-21 days	0	0

Table 21. Duration of Exposure to CAZ-AVI (by indication) - Adult Clinical Study Population (Safety Analysis Set)

Duration of exposure	Persons	Person time (Patient days)
>21 days	0	0
Total		4155

Sources: Tables R.2.1.3, R.2.1.4, and R.2.1.5.
CAZ-AVI = Ceftazidime-Avibactam; cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated urinary tract infection; HAP Hospital-acquired pneumonia.
a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions).
Note: Exposure = ['Stop date and time of last infusion' - 'Start date and time of first infusion' rounded down to an integer number of days] + 1. No randomised, blinded CAZ-AVI studies included an open-label extension.

Table 22. Duration of Exposure to CAZ-AVI (totals) - Adult Clinical Study Population (Safety Analysis Set)

Duration of exposure	Persons	Person time (Patient days)
Total patient population (Studies NXL104/1001; NXL104/1002; D4280C00007; D4280C00009; D4280C00010; D4280C00011; D4280C00012; D4280C00020; D4280C00023; NXL104/2001; NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE]; D4280C00018 [RECLAIM3]); D4281C00001 [REPROVE])		
1 day	92	92
2-4 days	182	588
5-10 days	1546	11430
11-14 days	399	5086
15-21 days	19	361
>21 days	0	0
Total		17557

Source: Table R.2.1.7.
CAZ-AVI = Ceftazidime-Avibactam.
a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions).
Note: Exposure = ['Stop date and time of last infusion' - 'Start date and time of first infusion' rounded down to an integer number of days] + 1. No randomised, blinded CAZ-AVI studies included an open-label extension.

Table 23. Duration of Exposure to CAZ-AVI – (by Indication) Paediatric Populations (From birth to < 3 months, and ≥3 months to <18 years)

Duration of exposure	cIAI (C3591004)#		cUTI (C3591005)#		C3591024 Part A		C3591024 Part B Gram negative infections*		Totals	
	Persons	Person time (Patient days)	Persons	Person time (Patient days)	Persons	Person time (Patient days)	Persons	Person time (Patient days)	Persons	Person time (Patient days)
1-4 days	11	38	43	150	25	25	9	26	88	239
5-7 days	24	148	21	129	0	0	7	48	52	325
8-10 days	23	202	2	18	0	0	2	19	27	239
11-15 days	3	37	1	11	0	0	3	35	7	83
Total	61	425	67	308	25	25	21	128	174	886

* Safety analysis set study C3591024 (Birth to <3 months of age). Part B patients received CAZ-AVI treatment for Gram-negative infections; Part A patients received a single dose only.

Safety analysis set data pool for studies D4280C00015 and D4280C00016 (3 months to < 18 years of age)

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Table 24. Exposure to CAZ-AVI by Dose (by Indication) - Adult Clinical Study Population (Safety Analysis Set)

Dose of exposure	Persons	Person time (Patient days)
cIAI (Studies NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00006 [REPRISE-cIAI]; D4280C00018 [RECLAIM3])		
2000 mg CAZ/500 mg AVI/500 mg MTZ	857[a]	6587
cUTI (Studies NXL104/2001; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE-cUTI])		
2000 mg CAZ/500 mg AVI	663	5454
500 mg CAZ/125 mg AVI	68	344
HAP (Study D4281C00001 [REPROVE])		
2000 mg CAZ/500 mg AVI	436	4155

Sources: Tables R.2.1.11, R.2.1.12, and R.2.1.10.
AVI = Avibactam; CAZ = Ceftazidime; CAZ-AVI = Ceftazidime-Avibactam; cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated Urinary Tract Infection; MTZ = Metronidazole.
a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions). These 2 patients are included in this table as it is known what study drug they received, although their exposure is unknown.
Note: No randomised, blinded CAZ-AVI studies included an open-label extension

Table 25. Exposure to CAZ-AVI by dose (totals) - Adult Clinical study population (safety analysis set)

Dose of exposure	Persons	Person time (Patient days)
Total patient population (Studies NXL104/1001; NXL104/1002; D4280C00007; D4280C00009; D4280C00010; D4280C00011; D4280C00012; D4280C00020; D4280C00023; NXL104/2001; NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE]; D4280C00018 [RECLAIM3]; D4281C00001 [REPROVE])		
3000 mg CAZ/2000 mg AVI	46	46
3000 mg CAZ/1000 mg AVI	21	62
2000 mg CAZ/500 mg AVI/500 mg MTZ	885	6699
2000 mg CAZ/500 mg AVI	1240	10398
1000 mg CAZ/250 mg AVI	8	8
500 mg CAZ/125 mg AVI	68	344

Source: Table R.2.1.14.
AVI = Avibactam; CAZ = Ceftazidime; CAZ-AVI = Ceftazidime-Avibactam; MTZ = Metronidazole.
a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions). These 2 patients are included in this table as it is known what study drug they received, although their exposure is unknown.
Note: No randomised, blinded CAZ-AVI studies included an open-label extension.

Table 26. Exposure to CAZ-AVI by dose (totals) (by Indication)– Paediatric Population (≥3 months to <18 years) (safety analysis set)

Dose of exposure	Persons	Person time (Patient days)
cIAI (C3591004)	**N = 61**	
2000 mg CAZ/500 mg AVI/500 mg MTZ	30 (49.2)	227
50 mg/kg CAZ/12.5 mg/kg AVI	31 (50.8)	198
40 mg/kg CAZ/10 mg/kg AVI	0	0
cUTI (C3591005)	**N = 67**	
2000 mg CAZ/500 mg AVI/500 mg MTZ	17 (25.4)	78
50 mg/kg CAZ/12.5 mg/kg AVI	45 (67.2)	213
40 mg/kg CAZ/10 mg/kg AVI	5 (7.5)	17

Table 1 subject by dose pediatric

Table 27. Exposure to CAZ-AVI by dose (totals) – Paediatric Population (from birth to < 3 months) (safety analysis set)

	C3591024 – Part A (single dose)		C3591024 – Part B (Gram negative bacterial infection	
Dose of exposure	**Persons**	**Person time (Patient days)**	**Persons**	**Person time (Patient days)**
C3591024	N = 25		N = 21	
30 mg/kg CAZ/7.5 mg/kg AVI[#]	9 (36.0)	9	8 (38.1)	51
20 mg/kg CAZ/5.0 mg/kg AVI*	16 (64.0)	16	16 (61.9)	77

Patients >28 days to <3 months old
* Patients with gestational age ≥37 weeks and ≤28 days old and gestational age ≥26 weeks to <37 weeks and ≤28 days.
Source: [redacted] SDTM Creation: 23JAN2023 (03:37) Source Data: ex Table Generation: 12OCT2023 (02:17) (Data cutoff date: 18JAN2023 Database snapshot date: 18JAN2023) Output File: ./CSR_Figaro/C3591024_RMP/adex_dose

Table 28. Exposure to CAZ-AVI by age group and gender (by indication) - Adult clinical study population (safety analysis set)

Age group	Persons		Person time (Patient days)	
	Male	Female	Male	Female
cIAI (Studies NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00006 [REPRISE-cIAI]; D4280C00018 [RECLAIM3])				
<18 years	0	0	0	0
18- <65 years	462	227	3514	1716
65- <75 years	59	48	494	408
75- <85 years	23	33	166	259
≥85 years	0	5	0	30
cUTI (Studies NXL104/2001; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE-cUTI])				
<18 years	0	0	0	0
18- <65 years	135	339	1141	2467
65- <75 years	66	67	561	543
75- <85 years	57	53	565	406
≥85 years	6	8	54	61
HAP (Study D4281C00001 [REPROVE])				
<18 years	0	0	0	0
18 - <65 years	159	41	1518	386
65 - <75 years	77	30	711	293
75 - <85 years	74	32	748	285
≥85 years	15	8	142	72

Sources: Tables R.2.1.17, R.2.1.18, and R.2.1.19
CAZ-AVI = Ceftazidime-Avibactam; cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated Urinary Tract Infection; HAP= Hospital-acquired pneumonia.
a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions). These 2 patients are included in this table as their various baseline characteristics are known, although their exposure is unknown.
Note: No randomised, blinded CAZ-AVI studies included an open-label extension.

Table 29. Exposure to CAZ-AVI by Age Group and Gender - Adult Clinical Study Population (Safety Analysis Set)

Age group	Persons		Person time (Patient days)	
	Male	Female	Male	Female
Total patient population (Studies NXL104/1001; NXL104/1002; D4280C00007; D4280C00009; D4280C00010; D4280C00011; D4280C00012; D4280C00020; D4280C00023; NXL104/2001; NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE]; D4280C00018 [RECLAIM3]; D4281C00001 [REPROVE])				
<18 years	0	0	0	0
18- <65 years	966	613	7036	4611
65- <75 years	202	145	1766	1244
75- <85 years	154	118	1479	950
≥85 years	21	21	196	163

Table 29. Exposure to CAZ-AVI by Age Group and Gender - Adult Clinical Study Population (Safety Analysis Set)

Age group	Persons		Person time (Patient days)	
	Male	Female	Male	Female

Source: Table R.2.1.21.
CAZ-AVI = Ceftazidime-Avibactam.
a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions). These 2 patients are included in this table as their various baseline characteristics are known, although their exposure is unknown.
Note: No randomised, blinded CAZ-AVI studies included an open-label extension.

Table 30. Duration of exposure to CAZ-AVI by Age Cohort (by Indication) – Paediatric population (≥3 months to <18 years) (Safety analysis set)

Age cohort	cIAI (C3591004)		cUTI (C3591005)	
	Persons	Person time (Patient days)	Persons	Person time (Patient days)
Cohort 1: 12 - <18 years	22	249	13	132
Cohort 2: 6 - <12 years	33	357	17	174
Cohort 3: 2 - <6 years	6	74	11	125
Cohort 4a: 1 - <2 years	0	0	12	144
Cohort 4b: 3 months - <1 year	0	0	14	162
Total	61	680	67	737

Source: Table R.2.1.11

Table 31. Duration of exposure to CAZ-AVI by Age Cohort – Paediatric population (from birth to <3 months) (Safety analysis set)

Age cohort	C3591024 – Part A (Single dose)		C3591024 – Part B (Gram negative bacterial infection)	
	Persons	Person time (Patient days)	Persons	Person time (Patient days)
>28 days* to <3 months	7	7	8	51
Full term to ≤ 28 days old	8	8	5	25
Premature to ≤ 28 days old	10	10	8	52
Total	25	25	21	128

*Includes term infants (GA ≥37 weeks) >28 days of age and preterm infants with corrected age >28 days. Corrected age = Subtract the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age was used only for determining eligibility of pre-term infants in Cohort 1. Actual age (chronological age) was used for determining eligibility of pre-term neonates in Cohort 3.
Source: [redacted] SDTM Creation: 23JAN2023 (03:37) Source Data: ex Table Generation: 12OCT2023 (06:38) (Data cutoff date: 18JAN2023 Database snapshot date: 18JAN2023) Output File: ./CSR_Figaro/C3591024_RMP/adex_cohort

Table 32. Exposure to CAZ-AVI by Age Group and Gender (by Indication) – Paediatric Population (≥3 months to <18 years) (Safety Analysis Set)

Age group	Persons		Person time (Patient days)		Persons		Person time (Patient days)	
	Male	Female	Male	Female	Male	Female	Male	Female
	cIAI (C3591004)				cUTI (C3591005)			
12 - <18 years	18	4	193	56	1	12	14	118
6 - <12 years	22	11	215	142	2	15	26	148
2 - <6 years	4	2	45	29	1	10	11	114
1 - <2 years	0	0	0	0	4	8	51	93
3 months - <1 year	0	0	0	0	3	11	32	130
Total	44	17	453	227	11	56	134	603

Source: Table R.2.1.18

Table 33. Exposure to CAZ-AVI by Age Group and Gender – Paediatric Population (from birth to <3 months) (Safety Analysis Set)

	C3591024 – Part A (single dose)				C3591024 – Part B (Gram negative bacterial infection)			
Age group	Persons		Person time (Patient days)		Persons		Person time (Patient days)	
	Male	Female	Male	Female	Male	Female	Male	Female
>28 days* to <3 months old	4	3	4	3	5	3	25	26
GA ≥37 weeks and ≤28 days old	4	4	4	4	4	1	24	1
GA ≥26 weeks to <37 weeks and ≤28 days old	2	8	2	8	2	6	19	33
Total	10	15	10	15	11	10	68	60

*Includes term infants (GA ≥37 weeks) >28 days of age and preterm infants with corrected age >28 days. Corrected age = Subtract the number of weeks born before 40 weeks of gestation from the chronological age. Corrected age was used only for determining eligibility of pre-term infants in Cohort 1. Actual age (chronological age) was used for determining eligibility of pre-term neonates in Cohort 3.
Source: [redacted] SDTM Creation: 23JAN2023 (03:37) Source Data: ex Table Generation: 12OCT2023 (03:10) (Data cutoff date : 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR_Figaro/C3591024_RMP/adex_agegrp

Table 34. Exposure to CAZ-AVI by Age Group and Gender (Totals) (by Indication) – Paediatric Population (Safety Analysis Set)

Age group	Persons		Person time (Patient days)	
	Male	Female	Male	Female
Total patient population (Studies: C3591004, C3591005)				
12 - <18 years	19	16	207	174
6 - <12 years	24	26	241	290
2 - <6 years	5	12	56	143
1 - <2 years	4	8	51	93
3 months - <1 year	3	11	32	130
Total	55	73	587	830

Source: Table R.2.1.18

Table 35. Exposure to CAZ-AVI by Racial Origin (by Indication) - Adult Clinical Study Population (Safety Analysis Set)

Racial origin	Persons	Person time (Patient days)
cIAI (Studies NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00006 [REPRISE-cIAI]; D4280C00018 [RECLAIM3])		
White	473	3653
Black or African American	7	52
Asian	331	2542
Native Hawaiian/Pacific Islander	0	0
American Indian/Alaska Native	6	61
Other	38	268
cUTI (Studies NXL104/2001; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE-cUTI])		
White	603	4942
Black or African American	5	25
Asian	60	363
Native Hawaiian/Pacific Islander	0	0
American Indian/Alaska Native	1	10
Other	62	458
HAP (Study D4281C00001 [REPROVE])		
White	181	1683
Black or African American	3	23
Asian	245	2390
Native Hawaiian/Pacific Islander	1	9
American Indian/Alaska Native	0	0
Other	6	50

Sources: Tables R.2.1.24, R.2.1.25, and R.2.1.26.

CAZ-AVI = Ceftazidime-Avibactam; cIAI = Complicated Intra-Abdominal Infection; cUTI = Complicated Urinary Tract Infection; HAP Hospital-acquired pneumonia.

a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions); these 2 patients are not counted in this table.

Note: No randomised, blinded CAZ-AVI studies included an open-label extension.

Table 36. Exposure to CAZ-AVI by Racial Origin (Totals) - Adult Clinical Study Population (Safety Analysis Set)

Racial origin	Persons	Person time (Patient days)
Total patient population (Studies NXL104/1001; NXL104/1002; D4280C00007; D4280C00009; D4280C00010; D4280C00011; D4280C00012; D4280C00020; D4280C00023; NXL104/2001; NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM[a]]; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE]; D4280C00018 [RECLAIM3]; D4281C00001 [REPROVE])		
White	1399	10926
Black or African American	53	208
Asian	668	5525
Native Hawaiian/Pacific Islander	1	9
American Indian/Alaska Native	7	71
Other	110	807

Source: Table R.2.28
CAZ-AVI = Ceftazidime-Avibactam.
a. Patients D4280C00001/E0201001 and D4280C00001/E5402001 received study treatment, but exposure could not be calculated programmatically because of missing data points (ie., start or end times/dates of infusions); these 2 patients are not counted in this table.
Note: No randomised, blinded CAZ-AVI studies included an open-label extension.

Table 37. Exposure to CAZ-AVI by Racial Origin (Totals) (by Indication) – Paediatric Population (≥3 months to <18 years) (Safety Analysis Set)

Racial origin	cIAI (C3591004)		cUTI (C3591005)		Totals	
	Persons	Person time (Patient days)	Persons	Person time (Patient days)	Persons	Person time (Patient days)
White	53	606	49	535	102	1141
Black or African American	0	0	0	0	0	0
Asian	7	72	12	145	19	217
Native Hawaiian or Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	1	2	1	2	2	4
Others	0	0	5	55	5	55
Total	61	680	67	737	128	1417

Source: Table R.2.1.25

Table 38. Exposure to CAZ-AVI by Racial Origin (Totals) – Paediatric Population (from birth to <3 months) (Safety Analysis Set)

Racial origin	C3591024 – Part A (single dose)		C3591024 – Part B (Gram negative bacterial infection)		Totals	
	Persons	Person time (Patient days)	Persons	Person time (Patient days)	Persons	Person time (Patient days)
White	18	18	18	104	36	122
Black or African American	2	2	2	21	4	23
Asian	4	4	1	3	5	7
Native Hawaiian or Pacific Islander	0	0	0	0	0	0
American Indian or Alaska Native	0	0	0	0	0	0
Not reported	1	1	0	0	1	1
Total	25	25	21	128	46	153

Source: [redacted] SDTM Creation: 23JAN2023 (03:37) Source Data: ex Table Generation: 13OCT2023 (04:15) (Data cutoff date : 18JAN2023 Database snapshot date : 18JAN2023) Output File: ./CSR_Figaro/C3591024_RMP/adex_race

Table 39. Exposure to CAZ-AVI by special populations (by indication) - Adult clinical study population (safety analysis set)

cIAI (Studies NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM]; D4280C00006 [REPRISE-cIAI]; D4280C00018 [RECLAIM3])		
	Persons	**Person time (Patient days)**
Renal impairment (baseline creatinine clearance)[a]		
≥81 mL/min	561	4178
51 – 80 mL/min	234	1908
31 – 50 mL/min	55	452
16 – 30 mL/min	2	15
6 – 15 mL/min	0	0
<6 mL/min	0	0
Hepatic impairment[b]		
Yes	48	375
No	809	6212
Cardiac impairment[c]		
Yes	75	579
No	782	6008
cUTI (Studies NXL104/2001; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE-cUTI])		
Renal impairment[a] (baseline creatinine clearance)		
≥81 mL/min	362	2777
51 – 80 mL/min	281	2310
31 – 50 mL/min	77	631
16 – 30 mL/min	5	52

Table 39. Exposure to CAZ-AVI by special populations (by indication) - Adult clinical study population (safety analysis set)

6 – 15 mL/min	3	17
<6 mL/min	0	0
Hepatic impairment[b]		
Yes	34	249
No	697	5549
Cardiac impairment[c]		
Yes	141	1153
No	590	4645
HAP (Study D4281C00001 [REPROVE])		
Renal impairment[a] (baseline creatinine clearance)		
≥81 mL/min	213	2007
51 – 80 mL/min	166	1607
31 – 50 mL/min	43	414
16 – 30 mL/min	12	108
6 – 15 mL/min	0	0
<6 mL/min	0	0
Hepatic impairment[b]		
Yes	64	628
No	372	3527
Cardiac impairment[c]		
Yes	108	1059
No	328	3096
Patients with limited treatment options - None		

a. For some patients, the degree of renal function at baseline could not be determined due to missing creatinine clearance data.

b. Baseline medical history was searched for MedDRA PTs as listed in Annex 7. Hepatic impairment was not necessarily defined with regard to hepatic function.

c. Baseline medical history was searched for MedDRA PTs as listed in Annex 7. Cardiac impairment was not necessarily defined with regard to cardiac function.

CAZ-AVI Ceftazidime-avibactam; cIAI Complicated intra-abdominal infection; cUTI Complicated urinary tract infection; HAP Hospital-acquired pneumonia, MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term.

Source: Tables R.2.1.32, R.2.1.33, and R.2.1.31.

Table 40. Exposure to CAZ-AVI by special populations (totals) - Adult clinical study population (safety analysis set)

Total patient population (Studies NXL104/1001; NXL104/1002; D4280C00007; D4280C00009; D4280C00010; D4280C00011; D4280C00012; D4280C00020; D4280C00023; NXL104/2001; NXL104/2002; D4280C00001 and D4280C00005 [RECLAIM]; D4280C00002 and D4280C00004 [RECAPTURE]; D4280C00006 [REPRISE]; D4280C00018 [RECLAIM3] D4281C00001 [REPROVE])		
	Persons	**Person time (Patient days)**
Renal impairment[a] (baseline creatinine clearance)		
≥81 mL/min	1350	9965
51 – 80 mL/min	683	5839
31 – 50 mL/min	175	1497
16 – 30 mL/min	19	175
6 – 15 mL/min	3	17
<6 mL/min	0	0
Hepatic impairment[b]		
Yes	146	1252
No	2094	16305
Cardiac impairment[c]		
Yes	324	2791
No	1916	14766

a. For some patients, the degree of renal function at baseline could not be determined due to missing creatinine clearance data.
b. Baseline medical history was searched for MedDRA PTs as listed in Annex 7, Hepatic impairment was not necessarily defined with regard to hepatic function.
c. Baseline medical history was searched for MedDRA PTs as listed in Annex 7, Cardiac impairment was not necessarily defined with regard to cardiac function.
CAZ-AVI Ceftazidime-avibactam; MedDRA Medical Dictionary for Regulatory Activities; PT Preferred term.
Source: Table R.2.1.35.

Table 41. Exposure to CAZ-AVI in cIAI and cUTI patients by special populations (by indication) – Paediatric population (≥3 months to <18 years) (Safety analysis set)

Renal impairment (mL/min/1.73 m^2) (baseline creatinine clearance	**cIAI (C3591004)**		**cUTI (C3591005)**		**Totals**	
	Persons	**Person time (Patient days)**	**Persons**	**Person time (Patient days)**	**Persons**	**Person time (Patient days)**
≥80	51	552	43	456	94	1008
50 - <80	9	113	23	269	32	382
30 - <50	0	0	1	12	1	12
<30	0	0	0	0	0	0
Missing	1	15	0	0	1	15
Hepatic impairment						
Yes	0	0	2	29	2	29
No	61	680	65	708	126	1388
Total	61	680	67	737	128	1417

Table 41. Exposure to CAZ-AVI in cIAI and cUTI patients by special populations (by indication) – Paediatric population (≥3 months to <18 years) (Safety analysis set)

Renal impairment (mL/min/1.73 m^2) (baseline creatinine clearance	cIAI (C3591004)		cUTI (C3591005)		Totals	
	Persons	Person time (Patient days)	Persons	Person time (Patient days)	Persons	Person time (Patient days)

Source: Table R.2.1.32
Renal impairment was defined by the reported Medical History terms using MedDRA PTs as listed in Annex 7

For study C3591024 (participants from birth to < 3 months) CrCL was not measured for enrolment, and dosing for moderate and severe renal impairment in this age group has not been established. (Participants with moderate or severe renal impairment were excluded from enrolment (defined by serum creatinine ≥2 times the ULN for age)).

Similarly, participants with hepatic impairment were excluded from enrolment (exclusion criteria were signs of viral hepatitis or acute hepatic failure).

Module SIV. Populations Not Studied in Clinical Trials

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

Table 42. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing information (Yes/No)	Rationale
Patient has past or current history of epilepsy or seizure disorders excluding febrile seizures of childhood.	Seizures have been reported with cephalosporins, metronidazole, and the other drugs used as comparators in CAZ-AVI studies including meropenem, imipenem cilastatin, moxifloxacin, and ciprofloxacin.	No	Patients with past or current history of epilepsy or seizure disorders excluding febrile seizures of childhood were included in the REPRISE study and therefore, based on the relevant data, no longer considered as missing information.
Severely impaired renal function (CrCl ≤ 30 mL/min; in REPROVE ≤16 mL/min) estimated by the Cockcroft-Gault formula.	This population was excluded from most clinical studies due to factors present in patients with significant renal disorders that confound the assessment of efficacy, safety, and tolerability. Additionally, exclusion of	No	"Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy" was included as missing information in RMP v 1.0 but was removed following

Table 42. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing information (Yes/No)	Rationale
Patient is receiving haemodialysis or peritoneal dialysis	this population would lend balance to the randomisation process, thereby allowing for objective analysis of final study results.		Regulatory Request to review topic (see Part II, SVII.2) in RMP v 3.2.
Evidence of significant hepatic disease determined by the following: history of acute hepatitis, chronic hepatitis, cirrhosis, acute hepatic failure, or acute decompensation of chronic hepatic failure, bilirubin >3× ULN, unless directly related to an acute infection or known Gilbert's disease, ALT or AST >3 × ULN, or ALP >3 × ULN unless the elevations are acute and directly related to an infectious process.	Cephalosporins have been associated with transient increases in liver enzymes; however, this population was excluded due to factors present in patients with severe hepatic disorders that confound the assessment of efficacy, safety, and tolerability. Additionally, exclusion of this population would lend balance to the randomisation process, thereby allowing objective analysis of final study results.	No	Patients with pre-existing significant hepatic impairment was included as missing information in RMP v 1.0 but was removed from v 3.2 following Regulatory Request to review topic (see Part II SVII.2).
Evidence of significant haematological disease determined by the following: haematocrit <25% or haemoglobin <8 g/dL, absolute neutrophil count <1000/mm^3 (in RECAPTURE, REPROVE, and REPRISE <500/mm3), or platelet count <75000/mm^3.	Cephalosporins have been associated with haematologic effects; however, this population was excluded due to factors present in patients with haematological disease that confound the assessment of efficacy, safety, and tolerability. Additionally, exclusion of this population would lend balance to the randomisation process, thereby allowing objective analysis of final study results.	No	AEs potentially related to haematological disorders representing low blood counts were assessed as adverse events of special interest in the clinical development program. The safety profile is expected to be the same in this population.

Table 42. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Criterion	Reason for Exclusion	Missing information (Yes/No)	Rationale
Evidence of significant immunologic disease determined by the following: Human immunodeficiency virus infection, with either a current Acquired Immune Deficiency Syndrome-defining condition (eg., Kaposi's sarcoma, *Pneumocystis carinii* pneumonia) or a CD4+ T lymphocyte count <200/mm^3 at the time of study entry, metastatic or haematological malignancy requiring chemotherapeutic interventions within 6 weeks prior to randomisation, and immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day of equivalent prednisolone).	This population was excluded due to factors present in patients with immunologic disease that confound the assessment of efficacy, safety, and tolerability. Additionally, exclusion of this population would lend balance to the randomisation process, thereby allowing objective analysis of final study results.	No	Topic is proposed to no longer being considered as missing information; refer to Part II, Section SVII.2 for rationale.
Women who are pregnant or nursing.	CAZ-AVI use was not studied in pregnant or nursing women.	No	Topic is proposed to no longer being considered as missing information; refer to Part II, Section SVII.2 for rationale.

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

Information presented in Table 43 is based on data from the cIAI, cUTI and HAP clinical studies only.

Table 43. Limitations of Adverse Drug Reaction Detection

Ability to detect adverse reactions	Limitation of study programme	Discussion of implications for target population
Which are rare (≥1/10000 to <1/1000); uncommon (≥1/1000 to <1/100)	Approximately 2238 subjects have been exposed to CAZ-AVI in the clinical development programme.	ADRs with a frequency greater than 1 in 750 could be detected if there were no background incidence.
Due to prolonged exposure	The longest duration of treatment studied in Phase 3 studies was 21 days for cIAI and cUTI, subjects and 14 days for HAP subjects; no subjects received CAZ-AVI for >21 days.	Due to the short duration of treatment, potential ADRs due to prolonged exposure were not captured in clinical studies.
Due to cumulative effects	The longest duration of treatment studied in Phase 3 studies was 21 days for cIAI and cUTI subjects and 14 days for HAP subjects; no subjects received CAZ-AVI for >21 days.	Due to the short duration of treatment, potential ADRs due to cumulative effects were not captured in clinical studies.
Which have a long latency	For the Phase 2 studies, the period of observation for adverse events was from the first dose up to 14 days after end of treatment (total of up to 28 days). For Phase 3 studies, the period of observation was from first dose up to and including the last visit (total of up to 49 days for cIAI up to 52 days for cUTI, and up to 32 days for HAP).	Due to the short duration of treatment and follow-up, potential ADRs due to long latency were not captured in clinical studies.

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

Due to the exclusion criteria (Table 42) and study design in the pivotal Phase 3 studies, the populations typically under-represented in the CAZ-AVI clinical study development programme are described below.

Table 44. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	In clinical studies, subjects were screened for pregnancy and excluded from participation if the pregnancy test was positive. In the CAZ-AVI clinical programme, 2 pregnancies occurred in 2 patients who were exposed to CAZ-AVI. One pregnancy resulted in a full-term, healthy baby; however, it is unlikely that the foetus was exposed to study drug

Table 44. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	as the last menstrual period was 8 days after end of treatment (EOT). The other pregnancy was electively terminated for non-medical reasons. Cephalosporins have not been studied extensively in pregnancy. Where a pregnancy classification system is applied, cephalosporins are commonly placed in the categories in which there are no adequate and well-controlled studies in pregnant women; however, either animal reproduction studies have failed to demonstrate a risk to the foetus or animal studies have shown an adverse effect, but limited or adequate studies in pregnant women have failed to demonstrate a risk to the foetus.[286] As noted in SmPC Section 4.6 (Fertility, pregnancy, and lactation) • Animal studies with CAZ do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. Animal studies with AVI have shown reproductive toxicity without evidence of teratogenic effects (see SmPC section 5.3). • CAZ-AVI should only be used in pregnancy if the potential benefit outweighs the possible risk. Use during pregnancy is proposed to be reclassified to no longer being considered as Missing Information and therefore is removed from the list of safety concerns (refer to Part II, Section SVII.2).
Breastfeeding women	CAZ and AVI are excreted in the breast milk of rats. Most cephalosporins are secreted to a small degree into breast milk, but as a class, they are considered compatible for use during breast-feeding.[287] As noted in SmPC Section 4.6 (Fertility, pregnancy, and lactation): • CAZ is excreted in human milk in small quantities. It is unknown whether AVI 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 CAZ-AVI therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Use during lactation is proposed to be reclassified to no longer being considered as Missing Information and therefore is removed from the list of safety concerns (refer to Part II, Section SVII.2).

Table 44. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with relevant comorbidities:	
Pre-existing significant hepatic disease	Mild to moderate hepatic impairment had no effect on the PK of CAZ in individuals administered 2 g IV q8h for 5 days, provided renal function was not impaired. Patients with pre-existing significant hepatic disease were not included in the clinical development program. 139 patients (in total in the adult phase 2/3 studies and 2 patients from the paediatric phase 2 studies with medical history of hepatic impairment were identified, however none had significant hepatic disease. The PK of CAZ in patients with severe hepatic impairment has not been established. The PK of AVI in patients with any degree of hepatic impairment has not been studied. Evidence of significant hepatic disease was an exclusion criterion for the Phase 3 studies. The PK of CAZ-AVI in patients with significant hepatic impairment has not been established. As CAZ-AVI does not appear to undergo significant hepatic metabolism, systemic clearance is not expected to be significantly affected by hepatic impairment. This was removed as missing information following Regulatory Request (see Part II SVII.2) in RMP v 3.2.
Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy	CAZ and AVI are eliminated via the kidneys. Elimination of CAZ and AVI is decreased in patients with moderate or severe renal impairment and ESRD, including patients undergoing haemodialysis. The CAZ-AVI dose should be reduced in patients with CrCl ≤ 50 mL/min according to the estimated CrCl range (CrCl ranges of 50 to 31, 30 to 16, 15 to 6, and <6 mL/min). Patients with severe renal impairment were excluded from Phase 3 and Phase 2 studies as follows: • Estimated CrCl ≤30 mL/min calculated by Cockcroft-Gault method [RECLAIM; RECLAIM3;[5] and RECAPTURE] • Estimated CrCl <6 mL/min calculated by Cockcroft-Gault method [REPRISE] • Patient with an estimated CrCl <50 mL/min by Cockcroft-Gault formula [Study 2002; Phase 2 cIAI]

[5] Protocol Amendment 3, dated 29 September 2014, revised the exclusion criterion to exclude patients with moderate renal impairment (CrCl>30 to ≤50 mL/min); prior to the amendment, patients with moderate renal impairment were eligible for the study.

Table 44. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	• Patient with an estimated CrCl ≤50 mL/min by Cockcroft-Gault formula [RECLAIM31] • Patients with an estimated CrCl <70 mL/min by Cockcroft-Gault formula [Study 2001; Phase 2 cUTI] • Patients with an estimated CrCl <16 mL/min by Cockcroft-Gault formula or patients expected to require haemodialysis or other renal support while on study therapy [REPROVE] Patient was receiving haemodialysis or peritoneal dialysis. Creatinine clearance (CrCl) <30 mL/min/1.73 m2 calculated using the child's measured height (length) and serum creatinine within the updated "bedside" Schwartz formula [ANDI and KURA]. Therefore, the percentage of subjects in the CrCl category of ≤30 mL/min (severe renal impairment) was small for adults: 1.1% (22 CAZ-AVI subjects across the adult Phase 2 and 3 studies, 22 patients (1.1%) taking CAZ-AVI had a baseline CrCl <= 30 ml/min (19 subjects/ 175 Patient Days CrCl 16-30 ml/min; 3 subjects/ 17 person days CrCl 6-15 ml/min), the majority of which were enrolled in the REPROVE study. No children in the paediatric Phase 2 studies had a CrCl category of <30 mL/min/1.73 m^2 and 0.8% (1 CAZ-AVI subject in the KURA study) had a CrCl category of ≥ 30 -< 50 mL/min/1.73 m^2 (moderate renal impairment). In Study 1003 (Phase 1), 6 subjects with severe renal impairment and another 6 patients subjects with ESRD received an IV infusion of 100 mg of AVI. Subjects from the ESRD cohort participated in 2 randomised sessions (during and between dialysis sessions) separated by a washout period of 7 to 14 days. Total clearance decreased by 6.5-fold in non-dialysed subjects with severe renal impairment. The decrease in total clearance was 14.3-fold in subjects with ESRD who were off dialysis. This was removed as missing information following Regulatory Request (see Part II SVII.2) in RMP v 3.2.
Patients with Other Relevant Co-Morbidity: Immunocompromised population	Not included in the clinical development program Certain potentially immunocompromised subjects were excluded from Phase 3 studies in order to remove bias that could impact the efficacy analysis as follows:

Table 44. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
	• Human immunodeficiency virus infection, with either a current Acquired immune deficiency syndrome-defining condition (eg., Kaposi's sarcoma, *Pneumocystis carinii* pneumonia) or a CD4+ T lymphocyte count <200/mm3 at the time of study entry (RECLAIM, RECAPTURE, RECLAIM3, and REPROVE) • Metastatic or haematological malignancy requiring chemotherapeutic interventions within 6 weeks prior to randomisation (RECLAIM, RECAPTURE, RECLAIM3 and REPROVE) • Immunosuppressive therapy including maintenance corticosteroid therapy (>40 mg/day of equivalent prednisolone) (RECLAIM, RECAPTURE, RECLAIM3 and REPROVE) • Illness (eg., significant immunosuppression) that, in the opinion of the investigator, may confound the results of the study or pose additional risks in administering the study drug to the patients (REPRISE) • Absolute neutrophil count <500/mm^3 (REPRISE, RECAPTURE and REPROVE). While the safety profile is expected to be similar to the general population, these patients are included here as the benefit risk profile may be different with respect to the benefit. The use in immunocompromised patients is proposed to be reclassified to no longer being considered as Missing Information and therefore is removed from the list of safety concerns (refer to Part II, Section SVII.2).

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

Cumulatively through 24 February 2025, it is estimated that 826,674 patients were exposed to CAZ-AVI worldwide.

Calculation of patient-years of exposure is based on the following assumptions:

Average daily dose is 2.5 g CAZ-AVI IV infusion every 8 hours for a total of 7.5 g CAZ-AVI per day.

- Patient treatment days are total grams of CAZ-AVI divided by 7.5.
- Patient treatment years are patient treatment days divided by 365.25.

Calculation of number of patients treated is based on the following assumptions:

- Mean treatment duration of 8.2 days, based on the CAZ-AVI clinical trials pooled data set.
- Patient treatment days divided by 8.2 gives the estimated number of patients treated.

SV.1.2. Exposure

Estimated exposure cumulative.

Table 45. Estimated exposure during the cumulative period

Region	Patient Treatment days	Patient-years	Number patients treated[a]	Total vials containing 2.5 g CAZ + AVI each
United States	1,201,439	3,289	146,517	3,604,316
European Union	2,023,585	5,540	246,779	6,070,755
Rest of the world	3,553,699	9,729	433,378	10,661,098
Total	6,778,723	18,558	826,674	20,336,169

a. Assuming 3 adult doses per day for 8.2-day course

Module SVI. Additional EU Requirements for the Safety Specification

Potential for misuse for illegal purposes

It is anticipated that CAZ-AVI will not be addictive in nature, and illegal misuse is not expected because CAZ-AVI is administered in a hospital setting. In addition, there is no evidence of withdrawal reactions in patients stopping CAZ-AVI. Therefore, the potential for misuse for illegal purposes is expected to be null.

Module SVII. Identified and Potential Risks

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

The following safety concerns were identified in the RMP v 1.0 dated April 2016 submitted at the time of the initial marketing authorisation (MA) application and approved by a Regulatory Authority (28 April 2016).

Table 46. Listing of Important Identified and Potential Risks in the Initial RMP Submission

Important identified risks	*Clostridium difficile*-associated diarrhoea (CDAD) Anaphylaxis and other severe hypersensitivity reactions
Important potential risks	Hepatotoxicity Superinfection (bacterial or fungal) Bacterial resistance development In patients with renal impairment, risk of neurological sequelae when the dose is not appropriately reduced

Table 46. Listing of Important Identified and Potential Risks in the Initial RMP Submission

Missing information	Pregnancy exposure Lactation exposure Pre-existing significant hepatic impairment Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy Immunocompromised population exposure

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

Not applicable.

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

Not applicable.

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

There were no new safety concerns.

Reclassification of safety concerns

"Anaphylaxis and other severe hypersensitivity reactions" and "*Clostridium difficile* associated diarrhoea (CDAD)" were reclassified from important identified risks, to risks not considered important in EU-RMP v. 2.0 and removed from the list of safety concerns.

The important potential risks "Superinfection (bacterial or fungal)" and "In patients with renal impairment, risk of neurological sequelae when the dose is not appropriately reduced" are reclassified to risks not considered important, and therefore are removed from the list of safety concerns in the RMP v 3.2 due to Regulatory Request during the assessment of the Type II c.I.6 variation application to add the indications cIAI, cUTI, HAP and LTO in children ≥3 months to <18 years to the SmPC.

"Superinfection (bacterial or fungal)" is reclassified as a potential risk not considered important for inclusion in the list of safety concerns in the RMP because it is an adverse reaction 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 and is a known risk that requires no further characterisation and is 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). No adverse reactions of superinfection have been received from the Zavicefta Clinical Development program or from post marketing sources as of 31 October 2018.

"In patients with renal impairment, risk of neurological sequelae when the dose is not appropriately reduced" is reclassified as a potential risk not considered important for inclusion in the list of safety concerns in the RMP because it is an adverse reaction 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 and is a known risk that requires no further characterisation and is 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). CAZ-AVI has clear instructions regarding dosing in renally impaired patients in the SmPC, and this toxicity was not identified in patients with renal impairment from the CAZ-AVI program. Moreover, this risk does not require additional pharmacovigilance activities or additional risk minimisation measures.

The missing information "Pre-existing significant hepatic impairment" and "Pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy" are removed from the list of safety concerns in RMP v 3.2 following Regulatory Request during the assessment of the Type II C.I.6 variation application to add the indication cIAI in children ≥3 months to ≤18 years to the SmPC.

Patients with severe hepatic impairment were excluded from clinical trials, and the medicinal product is not contraindicated in this population. 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. Therefore, further data collection/ studies in this population are not considered warranted.

Patients with pre-existing severe renal impairment including experience in haemodialysis/peritoneal dialysis and other renal replacement therapy were excluded in the CAZ-AVI clinical trials (see Section SIV.1). On Regulatory Request by PRAC Rapporteur to reconsider whether this missing information should be maintained, and in the context of the reclassification of "In patients with renal impairment, risk of neurological sequelae when the dose is not appropriately reduced" as a potential risk not considered important for inclusion in the list of safety concerns in the RMP, it was concluded that, when the dose is appropriately reduced as is presented in the SmPC, the safety profile has not been shown to differ from that characterised so far, based on routine pharmacovigilance in 5 years since the International Birth Date. As a safety concern has not been identified in this population, and routine pharmacovigilance is sufficient to monitor this population, it has been removed from the EU-RMP as missing information.

The Important Potential Risk of Bacterial resistance development is proposed to be reclassified as a potential risk, not considered important for inclusion in the list of the Safety concerns in the RMP. The risk of Bacterial resistance development is generally known and well understood by healthcare professionals for antibiotics, including CAZ-AVI. The risk is well characterized. The CAZ-AVI labelling indicates that it should be prescribed with consideration to official guidance on the appropriate use of antibacterial agents (i.e., in line with antimicrobial stewardship considerations).

The related additional PhV commitment (ie, to submit annual surveillance reports on bacterial resistance development for 5 years after the initial MA in the EU) has been fulfilled in 2023 and the last (fifth) surveillance report was submitted with PSUR #10 (reporting period 25 Feb 2022 through 24 Feb 2023). Based on the findings from the past 5 years, there were no unexpected levels of resistance identified to date. The MAH will continue to monitor bacterial resistance development as part of routine PhV activities, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorised).

The topics of "Pregnancy exposure" and "Lactation Exposure" are proposed to no longer be considered as Missing Information. Whilst there is limited data available on these topics, given CAZ-AVI has been marketed in the EU for 8 years and no new safety information has been identified from post marketing data, there is no reasonable expectation that the existing or future pharmacovigilance activities would further characterise the safety profile of the product with respect to these topics of Missing Information.

The topic "Immunocompromised population exposure" is proposed to no longer be considered as Missing Information. Successful use of CAZ-AVI in immunocompromised patients has been described in the scientific literature by various authors.[288-294] The adverse events reported in these patients is in line with the known safety profile for CAZ-AVI, and overall, no new safety information has been identified in this patient population. Furthermore, given CAZ-AVI has been marked in the EU for 8 years it is not reasonably expected that existing or future pharmacovigilance activities would further characterise the safety profile of the CAZ-AVI in this patient population.

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

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

Important identified risks

There are no important identified risks for CAZ-AVI.

Important Potential Risks

The following safety concern is considered an important potential risk:

- Hepatotoxicity

Clinical data presented in Table 24 to Table 28 are based on the data pooling strategy presented in Table 47.

Table 47. Data pooling for potential risk tables

Patient Population	Study Numbers
Phase 2 and 3 studies (Adults)	
cIAI	NXL104/2002; D4280C00001 and D4280C00005 (RECLAIM); D4280C00006 (REPRISE-cIAI); D4280C00018 (RECLAIM3)
cUTI	NXL104/2001; D4280C00002 and D4280C00004 (RECAPTURE); D4280C00006 (REPRISE-cUTI)
HAP	D4281C00001 (REPROVE)
Paediatric population (≥3 months to < 18 years of age)	
cIAI	C3591004 (ANDI)
cUTI	C3591005 (KURA)
Paediatric population birth to < 3 months of age	
Gram -negative bacterial Infection	C3591024 (NOOR) (single study – unpooled).
Phase 1 studies (Adults)	
Healthy volunteers	NXL104/1001; NXL104/1002; D4280C00007; D4280C00009; D4280C00010; D4280C00011; D4280C00012; D4280C00020; D4280C00023

SVII.3.1.1. Important Potential Risk: Hepatotoxicity

Hepatotoxicity that reflects a serious liver injury caused by drugs is a potential risk for CAZ-AVI because mild, transient elevations in hepatic transaminase levels have been associated with cephalosporin use and abnormal elevations of serum biomarkers of liver function have been reported amongst patients with cIAI, cUTI, and HAP disorders which are indications for CAZ-AVI.

To identify possible events of hepatotoxicity, a wide search for AEs with any potential hepatic association was conducted on the clinical data pool, and the results are summarised in Table 48. Additionally, clinical chemistry results for ALT, AST, and total bilirubin at any time up the last visit and cases that fulfilled Potential Hy's Law criteria at any time up to the last visit were reviewed to assess for the presence of hepatotoxicity. Medical review of the cases found was performed to identify actual events of hepatotoxicity, if any.

Table 48. Important Potential Risk: Hepatotoxicity

Potential mechanisms
Mild transient elevations in hepatic transaminase levels have been associated with cephalosporin use; however, hepatotoxicity is considered rare. The mechanism of toxicity is most likely idiosyncratic. [295] AVI is a novel β lactamase inhibitor with no evidence of Cytochrome P450 enzyme induction or inhibition to date.
Evidence source and strength of evidence
Clinical studies recognised class effects, and medical/scientific literature. The incidence of AEs representing possible events of hepatotoxicity in clinical studies was generally balanced across treatment groups. No cases fulfilled Hy's Law criteria and no cases of hepatotoxicity were identified. No SAEs of hepatoxicity have been reported in the paediatric clinical studies.

Table 48. Important Potential Risk: Hepatotoxicity

Considering the totality of the available clinical data, there is currently insufficient evidence of a causal relationship between hepatotoxicity and CAZ-AVI.

Characterisation of the risk

Patient population	No. (%)
cIAI clinical studies[a]	
CAZ-AVI+MTZ (N=857)	29 (3.4)
Comparator (N=863)	38 (4.4)
cUTI clinical studies[b]	
CAZ-AVI (N=731)	10 (1.4)
Comparator (N=729)	10 (1.4)
HAP clinical study[c]	
CAZ-AVI (N=436)	35 (8.0)
Meropenem (N=434)	31 (7.1)
Phase 1, healthy volunteer clinical studies[d]	
CAZ-AVI (N=216)	2 (0.9)
CAZ-AVI+MTZ (N=28)	0 (0)
Placebo (N=76)	1 (1.3)

Source: Tables R.1.9.1 and R.1.9.2.

a. cIAI clinical studies included Study NXL104/2002, RECLAIM, REPRISE-cIAI, and RECLAIM3. Comparators for the cIAI studies were meropenem and BAT.
b. cUTI clinical studies included Study NXL104/2001, REPRISE-cUTI, and RECAPTURE. Comparators for the cUTI studies were BAT, doripenem, and imipenem cilastatin.
c. HAP clinical study included Study D4281C00001 (REPROVE).
d. Phase 1, healthy volunteer clinical studies included Studies 1001, 1002, 007, 009, 010, 011, 012, 020, and 023.

In paediatric participants (from birth to < 18 years of age) there were 0 cases identified matching the search criteria provided are indicated at the bottom of these tables (also see Annex 7).

Frequency/Seriousness/Outcomes

Outcomes of AEs related to hepatotoxicity						
Patient population	**Resolved No. (%)**	**Resolving No. (%)**	**Resolved with sequelae No. (%)**	**Not resolved No. (%)**	**Fatal No. (%)**	**Total No. of subjects with SAEs No. (%)**
cIAI clinical studies[a]						
CAZ-AVI+ MTZ[d] N=857	35 (71.4)	6 (12.2)	1 (2.0)	3 (6.1)	0 (0)	2 (0.2)
Comparator[e] N=863	61 (88.4)	4 (5.8)	0 (0)	2 (2.9)	0 (0)	2/ (0.2)
cUTI clinical studies[b]						
CAZ-AVI[f] N=731	4 (30.8)	0 (0)	0 (0)	7 (53.8)	0 (0)	0 (0)
Comparator N=729	17 (100.0)	0 (0)	0 (0)	0 (0.0)	0 (0)	0 (0)
HAP clinical study[c]						
CAZ-AVI N=436	35 (68.6)	11 (21.6)	0 (0)	5 (9.8)	0 (0)	3 (0.7)
Meropenem N=434	36 (66.7)	7 (13.0)	0 (0)	11 (20.4)	0 (0)	0 (0.0)

Table 48. Important Potential Risk: Hepatotoxicity

Phase 1, healthy volunteer clinical studies[c]						
CAZ-AVI N=216	0 (0)	0 (0)	0 (0)	2 (100.0)	0 (0)	0 (0)
CAZ-AVI+MTZ N=28	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Placebo (n=76)	0 (0)	0 (0)	0 (0)	1 (100.0)	0 (0)	0 (0)

Source: Tables R.1.10.1, R.1.10.2, R.1.11.1, and R.1.11.2.

a. cIAI clinical studies included Study NXL104/2002, RECLAIM, REPRISE-cIAI, and RECLAIM3. Comparators for the cIAI studies were meropenem and BAT.

b. cUTI clinical studies included Study NXL104/2001, REPRISE-cUTI, and RECAPTURE. Comparators for the cUTI studies were BAT, doripenem, and imipenem cilastatin.

c. HAP study included REPROVE.

d. Phase 1, healthy volunteer clinical studies included Studies 1001, 1002, 007, 009, 010, 011, 012, 020, and 023. There were 7 (10.0%) subjects in the CAZ-AVI+MTZ group with AEs with unknown outcomes.

e. There were 2 (2.3%) subjects in the comparator group with AEs with unknown outcomes.

f. There were 2 (11.8%) subjects in the CAZ-AVI group with AEs with unknown outcomes.

Severity and nature of risk

Patient population	Mild No. (%)	Moderate No. (%)	Severe No. (%)
cIAI clinical studies[a]			
CAZ-AVI+MTZ (n=49 AEs)	33 (67.3)	15 (30.6)	1 (2.0)
Comparator (n=69 AEs)	43 (62.3)	24 (34.8)	2 (2.9)
cUTI clinical studies[b]			
CAZ-AVI (n=13 AEs)	12 (92.3)	1 (7.7)	0 (0)
Comparator (n=17 AEs)	13 (76.5)	4 (23.5)	0 (0)
HAP clinical study[c]			
CAZ-AVI (n=51 AEs)	33 (64.7)	15 (29.4)	3 (5.9)
Meropenem (n=54 AEs)	40 (74.1)	11 (20.4)	3 (5.6)
Phase 1, healthy volunteer clinical studies[c]			
CAZ-AVI (n=2 AEs)	2 (100.0)	0 (0)	0 (0)
CAZ-AVI+MTZ (n=0 AEs)	0 (0)	0 (0)	0 (0)
Placebo (n=1 AE)	1(100.0)	0 (0)	0 (0)

Source: Tables R.1.12.1 and R.1.12.2.

a. cIAI clinical studies included Study 2002, RECLAIM, REPRISE-cIAI, and RECLAIM3. Comparators for the cIAI studies were meropenem and BAT.

b. cUTI clinical studies included Study 2001, REPRISE-cUTI, and RECAPTURE. Comparators for the cUTI studies were BAT, doripenem, and imipenem cilastatin.

c. Phase 1, healthy volunteer clinical studies included Studies 1001, 1002, 007, 009, 010, 011, 012, 020, and 023.

Table 48. Important Potential Risk: Hepatotoxicity

Potential Hy's Law (maximum ALT ≥3×ULN or maximum AST ≥3×ULN and maximum total bilirubin ≥2×ULN) at any time up to the last visit

Patient population	Maximum ALT ≥3×ULN or maximum AST ≥3×ULN and maximum total bilirubin ≥2×ULN at any time
cIAI clinical studies[a]	
CAZ-AVI+MTZ (N [%])	16 (1.9)
Comparator (N [%])	17 (2.0)
cUTI clinical studies[b]	
CAZ-AVI+MTZ	1 (0.1)
(N [%])	1 (0.1)
HAP clinical study[c]	
CAZ-AVI	10 (2.3)
(N [%])	12 (2.8)
Phase 1, healthy volunteer clinical studies[d]: None	
Paediatric Clinical StudyStudies: **From ≥3 months to < 18 years**[e]**:** 0 cases **From birth to < 3 months**[f]**:** 0cases	

Source: Tables R.1.22.1 and R.1.22.2.

a. cIAI clinical studies**:** No subjects met Hy's Law criteria.
b. cUTI clinical studies: No subjects met Hy's Law criteria.
c. HAP clinical study: No subjects met Hy's Law criteria.
d. Phase 1, healthy volunteer clinical studies: No subjects met Hy's Law criteria.
e. Studies C3591004 and C3591005 in ≥3 months to < 18 years: No subjects met Hy's Law criteria.
f. Study C3591024 from birth to < 3 months of age: No subjects met Hy's Law criteria.

Post-marketing data from safety database

Cumulative Safety Database Experience (non-CT Cases)

In the post-marketing experience, through 24 February 2025, 52 cases were received by the MAH corresponding to 1.7% of the total PM cases received cumulatively. Distribution of event by seriousness and clinical outcome is provided below:

PT	No. of Events (% of Total PTs)	No. Serious Events (% of PT)	No. Events with Criterion of Hospitalization (% of PT)	Distribution of Events by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	53 (100)	52 (98.1)	20 (37.7)	3 (5.7)	31 (58.5)	0	2 (3.8)	17 (32.1)
Drug-induced liver injury	14 (26.4)	14 (100)	6 (42.9)	0	10 (71.4)	0	1 (7.1)	3 (21.4)
Hepatic cytolysis	11 (20.8)	11 (100)	5 (45.5)	0	8 (72.7)	0	0	3 (27.3)
Liver injury	8 (15.1)	8 (100)	2 (25)	0	3 (37.5)	0	0	5 (62.5)
Hepatic failure	4 (7.5)	4 (100)	2 (50)	1 (25)	0	0	1 (25)	2 (50)
Hepatocellular injury	4 (7.5)	4 (100)	1 (25)	0	4 (100)	0	0	0

Table 48. Important Potential Risk: Hepatotoxicity

Mixed liver injury	3 (5.7)	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)	0	0	1 (33.3)
Acute hepatic failure	1 (1.9)	1 (100)	0	0	0	0	0	1 (100)
Hepatitis	2 (3.8)	2 (100)	0	0	2 (100)	0	0	0
Liver disorder	2 (3.8)	1 (50)	1 (50)	0	1 (50)	0	0	1 (50)
Ascites	1 (1.9)	1 (100)	0	0	0	0	0	1 (100)
Asterixis	1 (1.9)	1 (100)	1 (100)	0	1 (100)	0	0	0
Hepatic cirrhosis	1 (1.9)	1 (100)	0	1 (100)	0	0	0	0
Hepatitis cholestatic	1 (1.9)	1 (100)	1 (100)	0	1 (100)	0	0	0

Cumulative Safety Database Experience (CT Cases)

In the cumulative period through 24 February 2025, a total of 4 CT case reports (involving only adult participants) of Hepatotoxicity (5.19% of the total CT cases received cumulatively) was received by the MAH. Distribution of event by seriousness and clinical outcome is provided below:

PT	No. of Events (% of Total PTs)	No Serious Events (% of PT)	No Events with Criterion of Hospitalization (% of PT)	Distribution of Events by Outcome N (%)				
				Fatal	Resolved / Resolving	Resolved with Sequelae	Not Resolved	Unknown / No Data
All PTs	4 (100)	4 (100)	1 (25)	0	3 (75)	0	1 (25)	0
Liver injury	2 (50)	2 (100)	0	0	2 (100)	0	0	0
Acute hepatic failure	1 (25)	1 (100)	0	0	0	0	1 (100)	0
Subacute hepatic failure	1 (25)	1 (100)	1 (100)	0	1 (100)	0	0	0

Risk factors and risk groups

History of alcohol use, hepatitis, and other pre-existing liver disease; concomitant use of hepatotoxic drugs; infections; age; sex; and daily drug dose.[296,297]

Preventability

Early medical diagnosis and intervention may help to prevent hepatotoxicity.[298] For patients with hepatic impairment, close monitoring of hepatic function should be considered, especially if CAZ-AVI is given in combination with hepatotoxic agents.

Impact on the risk-benefit balance of the product

The majority of patients with symptomatic, acute hepatotoxicity are expected to recover completely after discontinuation of the suspected drug. Hepatotoxicity patients with jaundice have worse prognoses than patients without drug-induced jaundice; however, most of the patients with jaundice will have a full recovery. Hepatotoxicity can lead to significant outcomes, such as acute liver failure, which may have fatal consequences or require liver transplantation.

Table 48. Important Potential Risk: Hepatotoxicity

Public health impact
There is a potential for increased costs due to the need for hospital care for liver failure however these are sporadic, and no public health impact is expected. Most studies have shown that the increase in liver enzymes due to antibiotic treatment is mild to moderate, and the majority of events do not require intervention.
MedDRA Search criteria*
SMQ (narrow scope) Drug related hepatic disorders - severe events only (including Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions and Hepatitis, non-infectious)

AVI = Avibactam; CAZ-AVI = Ceftazidime-Avibactam
* Taking experience from post marketing, the search criteria for this topic were adjusted to focus on severe hepatoxicity events only, and not present reports of less severe events such as asymptomatic liver parameter abnormalities.

SVII.3.2. Presentation of the Missing Information

There is no proposed Missing Information for CAZ-AVI.

Module SVIII. Summary of the Safety Concerns

Table 49. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	Hepatotoxicity
Missing information	None

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

III.1. Routine Pharmacovigilance Activities

Pfizer employs routine PhV consistent with the International Conference on Harmonisation E2E PhV Planning Guideline. Pfizer's standard processes and systems for collecting and recording information about all events potentially related to drug/product safety and for expedited and periodic reporting are in compliance with current local regulations and defined in globally applied Pfizer Standard Operating Procedures.

A comprehensive description of all aspects of the Pfizer PhV system is provided in the PhV System Master File, which is available upon request.

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- Standard topic for discussion in PSUR
- AEs of special interest 'TME" list for events of special interest requiring close surveillance
- Targeted follow-up questionnaire for post-marketing reports (see Annex 4).

Other forms of routine pharmacovigilance activities:

- Microbiologist participation in Risk management committee (Bacterial resistance development).

III.2. Additional Pharmacovigilance Activities

None.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Not applicable.

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

V.1. Routine Risk Minimisation Measures

For CAZ-AVI, no safety concerns have been identified for which actions other than routine risk minimisation activities are necessary. For the important potential risk, Table 50 presents a summary of planned risk minimisation activities.

Product information, in the form of the SmPC, will be the primary tool used to communicate information about the risks associated with the use of CAZ-AVI. The SmPC contains relevant information on indication, efficacy, dosing, contraindications, warnings, precautions, and adverse reactions, as well as dosing limitations in special populations to prevent or minimise risks.

For the potential safety concerns, the SmPC is considered sufficient to communicate risk. Subjects in the clinical development program were closely monitored to identify and characterise AEs of special interest and any new emerging safety signal. No additional risk minimisation measures are planned for the important potential risk. The need for risk minimisation measures will be assessed whenever the safety specification is updated.

Table 50. Description of routine risk minimisation measures by safety concern

Safety Concern[a]	Routine risk minimisation activities
Hepatotoxicity	Routine risk communication: SmPC Section 4.2 (Posology and method of administration) SmPC Section 4.8 (Undesirable effects) SmPC Section 5.2 (Pharmacokinetic properties)
	Routine risk minimisation activities recommending specific clinical measures to address the risk: Posology and method of administration for hepatotoxicity are included in SmPC Section 4.2 and dose adjustment in Section 5.2. Undesirable effects associated with hepatotoxicity are included in SmPC section 4.8.

a. Reclassification of missing information is presented in PART II.SVII.2.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities as described in V.1 are sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures are proposed.

V.3. Summary of Risk Minimisation Measures

Table 51. Summary Table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety Concern[a]	Risk Minimisation Measures	Pharmacovigilance Activities
Important potential risks		
Hepatotoxicity	Statements within SmPC Sections 4.2 (Posology and method of administration), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties) No additional RMMs.	Routine PhV activities beyond adverse reactions reporting and signal detection: targeted FU questionnaire for post-marketing reports related to hepatoxicity. Additional PhV activities: None

a. Reclassification of missing information is presented in PART II.SVII.2.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Zavicefta (Ceftazidime-Avibactam)

This is a summary of the RMP for Zavicefta. The RMP details important risks of Zavicefta, how these risks can be minimised, and how more information will be obtained about Zavicefta ′s risks and uncertainties (missing information).

Zavicefta ′s SmPC and its package leaflet give essential information to healthcare professionals and patients on how Zavicefta should be used.

This summary of the RMP for Zavicefta 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 EPAR's RMP.

I. The Medicine and What It Is Used For

Zavicefta is authorised for the treatment of Complicated Intra-Abdominal Infection, Complicated Urinary Tract Infection, including pyelonephritis, Hospital-Acquired Pneumonia including Ventilator-Associated Pneumonia, and for the treatment of infections due to aerobic Gram-negative organisms in adult patients with limited treatment options (See SmPC for the full indication). It contains ceftazidime and avibactam as the active substances, and it is given intravenously. Zavicefta is authorised for the treatment of Complicated Intra-Abdominal Infection, Complicated Urinary Tract Infection, including pyelonephritis, Hospital-acquired Pneumonia, including ventilator associated pneumonia and Infections due to aerobic Gram-negative organisms in patients with limited treatment options from birth and above.

Further information about the evaluation of Zavicefta ′s benefits can be found in Zavicefta ′s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004027/human_med_001993.jsp&mid=WC0b01ac058001d124

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

Important risks of Zavicefta together with measures to minimise such risks and the proposed studies for learning more about Zavicefta '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 public (eg., 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 AEs is collected continuously and regularly analysed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Zavicefta is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of Zavicefta 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 Zavicefta.

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 (eg., on the long-term use of the medicine).

Table 52. List of important risks and missing information

Important potential risks	Hepatotoxicity
Missing information	None

II.B. Summary of Important Risks

There are no safety concerns considered important identified risks.

Table 53. Important Potential Risk - Hepatotoxicity

Evidence for linking the risk to the medicine	Clinical studies, recognised class effects, and medical/scientific literature. The incidence of AEs representing possible events of hepatotoxicity was generally balanced across treatment groups in the clinical studies. No cases fulfilled Hy's Law criteria and no cases of actual hepatotoxicity were identified.
Risk factors and risk groups	History of alcohol use, hepatitis, and other pre-existing liver disease; concomitant use of hepatotoxic drugs; infections; age; gender; and daily drug dose.[296,297]

Table 53. Important Potential Risk - Hepatotoxicity

Risk minimisation measures	Routine risk minimisation measures Statements within SmPC Sections 4.2 (Posology and method of administration), 4.8 (Undesirable effects), and 5.2 (Pharmacokinetic properties). No additional risk minimisation measures.

II.C. Post-Authorisation Development Plan

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

Currently there are no studies which are conditions of the EU marketing authorisation of CAZ-AVI.

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

There are no studies required for CAZ-AVI.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme.

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan.

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

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CEFTAZIDIME-AVIBACTAM (ZAVICEFTA)
HEPATIC EVENT DATA CAPTURE AID

The questions provided in this section are intended to better evaluate hepatic events in patients treated with ceftazidime-avibactam.

1. Please mark whether the patient experienced any of the following around the time of the hepatic event:

☐ Fever
☐ Asthenia
☐ Anorexia
☐ Abdominal pain
☐ Vomiting
☐ Splenomegaly
☐ Hepatomegaly
☐ Lymphadenopathy
☐ Cutaneous symptoms (e.g., rash, pruritus, purpura)
☐ Arthralgia
☐ Confusion
☐ Ascites
☐ Jaundice
☐ Coma
☐ Other, please specify:

2. Please mark whether the patient was taking any of the following medications / substances at the time of the adverse event or prior to the onset of the adverse event:

☐ Other antibiotics
☐ Antivirals
☐ NSAIDs
☐ Statins
☐ Oral contraceptives
☐ Chlorpromazine
☐ Halothane☐ Heart or blood pressure medications (e.g., beta blockers, ARBs, PDE5 inhibitors, anti-arrhythmic drugs)
☐ Diuretics
☐ Anticoagulants
☐ Immunosuppressants / glucocorticoids (cyclosporine, antibodies, DMARDs)
☐ Over-the-counter drugs / herbal preparations (e.g., wild mushrooms)
☐ Recreational drugs (e.g., cocaine)

3. Please mark whether the patient had any of the following risk factors or conditions that may have contributed to the hepatic event:

☐ Hepatobiliary disorder
☐ Auto-immune disease
☐ Blood transfusion
☐ Obesity
☐ Sexually transmitted disease
☐ Occupational toxic agent
☐ Obtained tattoo, acupuncture, or piercing
☐ Recent vaccinations or travels

If yes, please specify:

4. Did the patient have a family history of liver disease (e.g., genetic conditions)?

☐ Yes ☐ No ☐ Unknown

If yes, please specify:

5. Does the patient drink alcohol?

☐ Yes ☐ No ☐ Unknown

If yes, please specify amount and frequency:

6. Was hepatic function test (e.g., AST, ALT, Bilirubin) performed at the following times? Please check all that apply.

☐ In year prior to start of drug ☐ At start of therapy ☐ During therapy ☐ After therapy
☐ None ☐ Unknown

If test was performed, please record the dates and relevant results in the laboratory data section.

7. Were any of the following laboratory tests performed?

Test	Date Performed	Results with units	Reference Range
Aspartate transaminase (AST)			
Alanine transaminase (ALT)			
Gamma-glutamyl transferase (GGT)			
Alkaline phosphatase (ALP)			
Creatine kinase (CPK)			
Total bilirubin (Direct/Indirect)			
Prothrombin time (PT)			
International normalized ratio (INR)			
Total protein			
Albumin			
Viral etiologies of hepatitis			
Anti-nuclear antibody (ANA)			

Anti-smooth muscle antibody (ASMA)			
Immunoglobulin G (IgG) level			
Medical imaging (e.g., ultrasound, CT, MRI, MRCP)			
Liver histology			

8. Were any other diagnostic tests performed related to the hepatic event (examples: serum a1-antitrypsin, ferritin, ceruloplasmin, cholangiogram, aFP etc.)? If yes, please provide the results.

Test	Date Performed	Results with units	Reference Range

Version History

Version	Version Date	Summary of Revisions
2.0	30-Jun-2025	Existing DCA modified to develop simplified version.
1.0	03-Oct-2022	Existing DCA converted to latest DCA format which includes questions relevant to product-event (or medical concept) pair.