Proposal to the 2025 WHO EML Expert Committee on AMR/AWaRe Classification regarding Cefoperazone/Sulbactam

Contents

Abbreviations and glossary

ATC code	Anatomical Therapeutic Chemical (ATC) classification system code. Active pharmaceutical substances are classified in a hierarchy with five different levels based on to the anatomical organ or system on which they act and their therapeutic, pharmacological, and chemical properties. The fifth level code corresponds to the individual chemical substance (medicine).
Core list	The core list presents essential medicines needed for a basic health care system. In most cases these are medicines used in the primary care setting.
Complementary list	The complementary list presents essential medicines for which specialized diagnostic or monitoring facilities, and/or specialist medical care, and/or specialist training are needed. Essential medicines may also be listed as complementary because of higher cost or less favourable cost-effectiveness. In most cases these are medicines used in secondary or tertiary care settings.
AWaRe	Access, Watch, Reserve
EML	WHO Model List of Essential Medicines
EMLc	WHO Model List of Essential Medicines for Children. The EMLc lists medicines for children up to and including 12 years of age.
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
ICD-11	International Classification of Diseases, 11th Revision
INN	International non-proprietary name. Medicines are listed in the EML and EMLc using their international nonproprietary names. Each INN is a unique name that is globally recognized and is public property.
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Square box listing	Square box listings are identified with the symbol "□" next to the listed medicine. This symbol indicates that therapeutic alternatives to the listed medicine may be considered for selection at the national level. Alternatives may be individual medicines, or multiple medicines within a pharmacological class or chemical subgroup, defined at the 4th level of the Anatomical Therapeutic Chemical (ATC) classification, which have similar clinical effectiveness and safety. The listed medicine should be the example of the class or subgroup for which there is the best evidence for effectiveness and safety or has some advantage in a relevant evaluation dimension (e.g., price). A square box is not used to indicate alternative generic brands of the same small molecule medicines, nor alternative biosimilars of biological medicines.

PROPOSAL FOR THE RECLASSIFICATION OF CEFOPERAZONE/SULBACTAM FOR ANTI-INFECTIVE TREATMENT FROM THE AWaRe CATEGORY "NOT RECOMMENDED" TO "WATCH"

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Section 1: Summary statement of the proposal

Cefoperazone/Sulbactam

There is a distinction between evidence-based fix dose combinations of antibiotics vs. non-evidence-based combinations. A vast majority of newly launched antibiotics are evidence-based fix dose combinations. With this in mind, we suggest there is value in reviewing the composition and rationale of the WHO's non-recommended antibiotics list.

Cefoperazone/Sulbactam is an evidence-based fix dose combination formulated based on pharmacology, pharmacodynamics, and clinical evidence. It effectively treats bacterial infections and delays the development of resistance through its broad-spectrum antibacterial and β-lactamase inhibition synergy.

Cefoperazone/Sulbactam exhibits antibacterial activity against all bacteria sensitive to cefoperazone. Additionally, it demonstrates synergistic effects against various bacteria, reducing the minimum inhibitory concentration (MIC) by up to fourfold compared to the individual components. Pharmacokinetics/Pharmacodynamics (PK/PD) studies indicate that the pharmacokinetics of the Cefoperazone/Sulbactam combination do not significantly differ from those of the individual products, suggesting no notable pharmacokinetic interaction between the combination and the individual drugs. In vitro surveillance shows that the resistance rates of Escherichia, Klebsiella, and Pseudomonas remained relatively stable in most countries over the years. Clinical research confirms that Cefoperazone/Sulbactam is effective and safe for treating infections and is recommended by guidelines in multiple countries for anti-infective therapy.

This proposal recommends the reclassification of Cefoperazone/Sulbactam from the "Not Recommended" list of antibiotics to the "Watch" category. Cefoperazone/Sulbactam plays a crucial role in treating infections caused by common Gram-negative bacteria, including E. coli, Klebsiella pneumoniae, Acinetobacter baumannii, and Pseudomonas aeruginosa. It is a guideline-recommended first-line treatment for infections caused by ESBL-producing Enterobacteriaceae.

Furthermore, Cefoperazone/Sulbactam is widely used to treat MDR bacterial infections and is recognized and utilized in many countries and regions worldwide. Multidrug-resistant (MDR) bacterial infections pose a significant global public health challenge, especially in healthcare facilities.

In this proposal, we consider the best available evidence comparing Cefoperazone/Sulbactam to other antibiotics in the treatment of common Gram-negative and MDR bacterial infections to demonstrate our request for reclassification. Additionally, we discuss its availability, cost, and cost-effectiveness in the countries/regions where it is currently available.

To analyze the overall trends in the resistance rates of pathogens to Cefoperazone/Sulbactam over different years, we organized and analyzed data from the ATLAS (Antimicrobial Testing Leadership and Surveillance) * database from 2018 to 2022. The data includes five countries: China, India, the Czech Republic, Japan, and Malaysia. Based on this analysis, and despite slight fluctuations in resistance rates of various pathogens over the years, the resistance rates of Acinetobacter, Escherichia, Klebsiella, and Pseudomonas in most countries remained stable. Since the countries in the sample represent a very significant portion of those where Cefoperazone/Sulbactam is currently in use (and of the global population), we conclude that the antibacterial effectiveness of Cefoperazone/Sulbactam has not been affected by increases in resistance over these years, demonstrating its sustained efficacy.

Additionally, routine surveillance data from the China CHINET Antimicrobial Resistance Surveillance Network (http://m.chinets.com) from 2014 to 2023 have been collected and analyzed. For the past decade, the resistance rates of Klebsiella spp., Escherichia coli, and Pseudomonas aeruginosa to Cefoperazone/Sulbactam have remained within a narrow range of fluctuation, with no significant increase.

This stability is partly because Cefoperazone/Sulbactam is an effective β-lactamase inhibitor combination. Cefoperazone and sulbactam have a synergistic effect, with sulbactam enhancing the antibacterial activity of cefoperazone. Additionally, stable rates of resistance may also be related to rational antibiotic usage policies, continuous antimicrobial surveillance, and varying antimicrobial treatment strategies across different countries.[1]

*ATLAS: A global program monitoring antimicrobial efficacy and resistance patterns to help optimize treatment strategies.

Section 2: Consultation with WHO technical departments

Pfizer has consulted with the following technical experts at WHO:

Dr. Lorenzo Moja, Scientist.

WHO Secretariat of the Selection and Use of Essential Medicines, WHO Essential Medicines and Health Products (EMP) Department.

Dr. Benedikt Huttner, Head of the Control and Response Strategies Unit.

WHO Antimicrobial Resistance Division.

Section 3: Other organization(s) consulted and/or supporting the submission

In preparing the submission for Cefoperazone/Sulbactam, we have consulted the following organizations and experts:

- KOL Name: **Mei Zeng**
- Affiliation: Department of Infectious Diseases, Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China.
- Relationship between the Organization and the Applicant: The relationship was limited to communication and consultation, with no involvement in the development or support of the submission.

Section 4: Key information summary for the proposed medicine(s)

INN

Cefoperazone/Sulbactam

ATC Code

J01DD62

Indication (Cefoperazone Sodium and Sulbactam Sodium for Injection Labeling Document（2：1）, 2024)

(Cefoperazone Sodium and Sulbactam Sodium for Injection Labeling Document（1：1）, 2024)

Monotherapy

Cefoperazone/sulbactam is indicated for the treatment of the following infections when caused by susceptible organisms:

- Respiratory Tract Infections (Upper and Lower)
- Urinary Tract Infections (Upper and Lower)
- Peritonitis, Cholecystitis, Cholangitis, and Other Intra-abdominal Infections
- Septicemia
- Meningitis
- Skin and Soft Tissue Infections
- Bone and Joint Infections
- Pelvic Inflammatory Disease, Endometritis, Gonorrhea, and Other Infections of the Genital Tract

Combination Therapy

Because of the broad spectrum of activity of cefoperazone/sulbactam, most infections can be treated adequately with this antibiotic alone. However, cefoperazone/sulbactam may be used concomitantly with other antibiotics if such combinations are indicated. If an aminoglycoside is used (see Interactions of Drugs, Incompatibilities, Aminoglycosides), renal function should be monitored during therapy.

ICD-11 Code

Dosage Form	Strength	EML	EMLc
Injection (1:1 ratio)	CEF 0.5 g + SUL 0.5 g	No	No
Injection (2:1 ratio)	CEF 1 g + SUL 0.5 g	No	No

ICD-11: 01 Certain infectious or parasitic diseases
This chapter includes certain conditions caused by pathogenic organisms or microorganisms, such as bacteria, viruses, parasites or fungi.
https://icd.who.int/browse/2024-01/mms/en#1435254666

Section 5: Listing as an individual medicine or representative of a pharmacological class / therapeutic group

Our proposal is to include Cefoperazone/Sulbactam under the "Watch" Category of the WHO AWaRe list, and to remove it from the “Non-Recommended” list, where it currently sits. The WHO AWaRe classification includes classes that have higher resistance potential and includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine and/or antibiotics that are at relatively high risk of selection of bacterial resistance. These medicines should be prioritized as key targets of stewardship programs and monitoring. Selected Watch group antibiotics are recommended as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes and are listed as individual medicines on the WHO Model Lists of Essential Medicines. (AWaRe classification of antibiotics for evaluation and monitoring of use, 2023, 2024).

On the other hand, the “non-recommended” list of antibiotics does not have stated scientific criteria or specifications for products currently included in it -which are mostly fixed dosed combinations. Since there is a distinction between evidence-based fix dose combinations of antibiotics vs. non-evidence-based combinations we suggest there is value in reviewing the composition and rationale of the WHO’s non-recommended antibiotics list. The case of Cefoperazone/Sulbactam, an evidence based fixed dose combination, serves as an example of the need for reconsideration.

Justification as a Representative Medicine in the Watch category of the AWaRe classification:

1.Cefoperazone/Sulbactam is an evidence-based fix dose combination formulated based on pharmacology, pharmacodynamics, and clinical evidence.

The antibacterial component of Cefoperazone/Sulbactam is Cefoperazone, a third-generation cephalosporin, which achieves its bactericidal effect by inhibiting the biosynthesis of peptidoglycan in the cell walls of susceptible bacteria during their growth phase. In addition to its antibacterial activity against Neisseriaceae and Acinetobacter species, sulbactam irreversibly inhibits many important β-lactamases produced by β-lactam antibiotic-resistant strains. Sulbactam can prevent the degradation of cephalosporin antibiotics by resistant bacteria, and it exhibits significant synergistic effects when combined with cephalosporins. Susceptible strains are generally more sensitive to the Cefoperazone/Sulbactam combination than to Cefoperazone alone. The Cefoperazone/Sulbactam combination exhibits synergistic antibacterial activity against various bacteria. (Cefoperazone Sodium and Sulbactam Sodium for Injection Labeling Document（2：1）, 2024) (Cefoperazone Sodium and Sulbactam Sodium for Injection Labeling Document（1：1）, 2024)

A published article by the anti-infection team from Huashan Hospital of Fudan University in China

comprehensively elucidates the pharmacokinetic and pharmacodynamic characteristics of Cefoperazone/Sulbactam. It summarizes the literature-reported strategies for optimizing dosing regimens for clinical use. Cefoperazone/Sulbactam, a classic fixed-dose combination drug that has been clinically applied in China for many years, shows no significant changes in pharmacokinetics when compared to the single drugs. The research findings indicate that when administered as a 3 g intravenous infusion over 15 minutes, Cefoperazone reaches a peak plasma concentration (Cmax) of 430.9 μg/mL and an area under the curve (AUC0-∞) of 356 μg·h/mL. Similarly, when administered as a 1.5 g intravenous infusion over 15 minutes, Sulbactam achieves a Cmax of 83.4 μg/mL and an AUC0-∞ of 77.7 μg·h/mL, as shown in the table below. When comparing the pharmacokinetic parameters of Cefoperazone and Sulbactam administered separately with those of an equal dose of Cefoperazone/Sulbactam administered simultaneously, no significant changes were observed, suggesting that the two drugs have no significant pharmacokinetic interaction when combined. (Liu xiaofen,et al.2022)

2. Recommendation Status in Treatment Guidelines

In treatment guidelines from China and India, Cefoperazone/Sulbactam and Piperacillin/Tazobactam are recommended equally for managing ESBL-producing infections of mild to moderate severity. Both drugs are listed as first-line options, particularly when carbapenems are not recommended or just as alternatives. In the Chinese guidelines, Cefoperazone/Sulbactam is recommended for treating mild to moderate community-acquired intra-abdominal infections, whereas Piperacillin/Tazobactam is used for *severe* community-acquired intra-abdominal infections. Although Piperacillin/Tazobactam has been included in the "Watch" category, Cefoperazone/Sulbactam's listing in the guidelines indicates its significance for the same indications. Furthermore, Cefoperazone/Sulbactam is classified as a highest priority critically important antimicrobial by WHO. (WHO, 2024)

3. Consistency and Differentiated Use

As mentioned above, both Piperacillin/Tazobactam and Cefoperazone/Sulbactam are recommended in existing guidelines, and while their indications are similar, they are not identical. Only Piperacillin/Tazobactam is listed under WHO's "Watch" category. Classifying Cefoperazone/Sulbactam in the "Watch" category and removing it from the non-recommended list would ensure comprehensive treatment options are available to patients in the regions where the product is available, addressing varied guidelines and usage scenarios.

4. Global Guideline Coverage: Listing Cefoperazone/Sulbactam in the "Watch" category would ensure that treatment options are consistent across different regions and guidelines, providing appropriate visibility to available alternatives to manage ESBL infections.

5. Comprehensive Representation: By proposing listing Cefoperazone/Sulbactam in the "Watch" category, we

aim to ensure diversity and balance in treatment options. This approach reflects the therapeutic roles played by different medicines recommended in guidelines.

Resistance patterns for Cefoperazone/Sulbactam

1.Overall Resistance Stability:

Data over several years shows that resistance rates for Cefoperazone/Sulbactam against various pathogens (such as Acinetobacter, Escherichia coli, Klebsiella pneumoniae, and Pseudomonas aeruginosa) remains relatively stable across different countries and regions. There has not been a significant increase in resistance, demonstrating its stability in the longer term.

2.Resistance Trends:

We selected sample countries based on a comprehensive consideration of the sales and geographic distribution of Cefoperazone/Sulbactam. Countries where Cefoperazone/Sulbactam has been marketed by Pfizer include China, India, the Czech Republic, Japan, and Malaysia. In these countries resistance to Cefoperazone/Sulbactam generally shows small fluctuations and no significant increase.

Observations on Specific Pathogens:

- Acinetobacter- In India, resistance remained stable from 2019 to 2021 but showed an upward trend in 2022.
- Escherichia coli- In India, resistance decreased slightly in 2019 but increased towards 2022.
- *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*- Resistance rates fluctuated within a certain range, without significant increases.

Resistance data for China (Fig. 1)

China is the country where Pfizer's Cefoperazone/Sulbactam is mostly used so the resistance rates of common gram-negative bacteria on China's CHINET is of critical significance. Based on resistance rates for China in different years (source: CHINET Data Cloud,2023) the resistance rates of *Escherichia coli, Pseudomonas aeruginosa,* Klebsiella spp., etc., to CEFOPERAZONE/SULBACTAM varied within a narrow range. Figures 2 to 5 show resistance trends for other countries between 2018-2022.

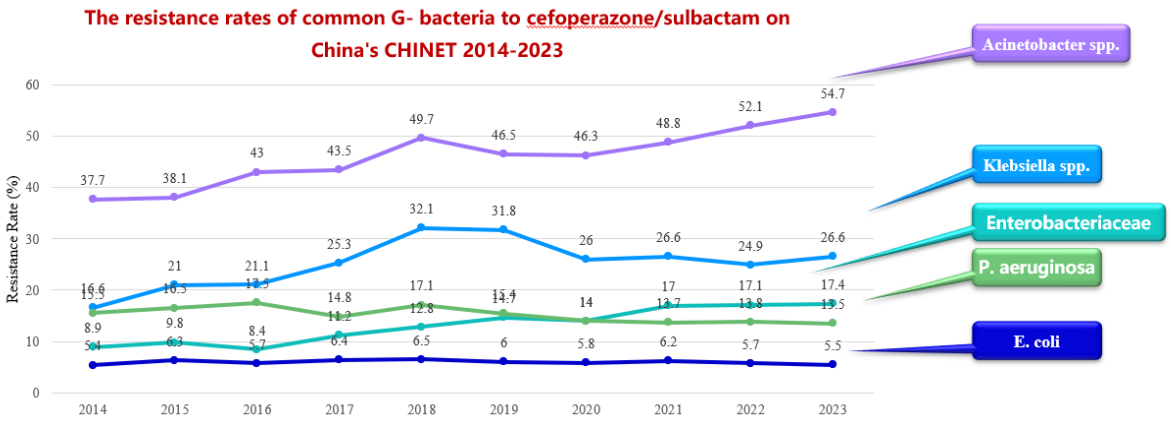

Figure 1 The resistance rates of common G- bacteria to cefoperazone/sulbactam on China's CHINET 2014-2023

ATLAS data (ATLAS, 2024)

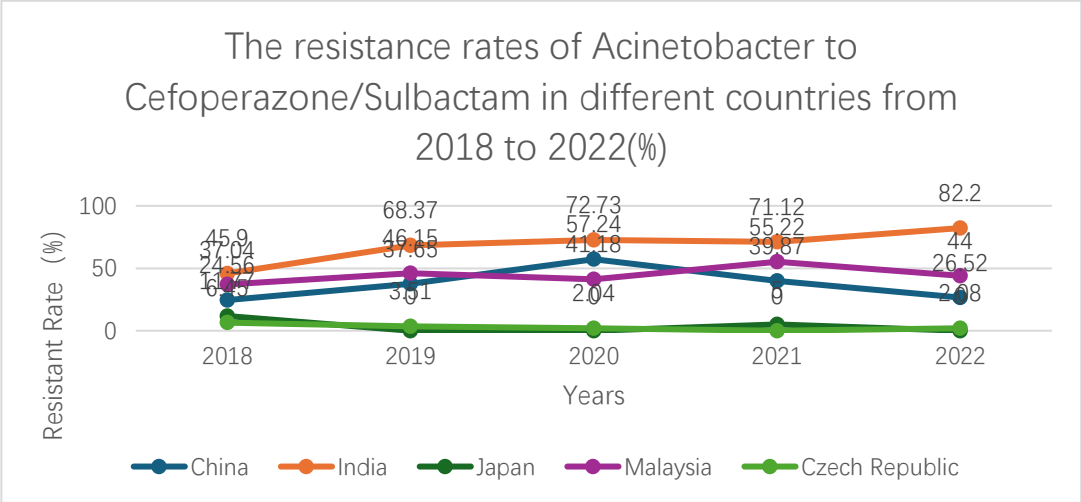

Figure 2 The resistance rates of Acinetobacter to Cefoperazone/Sulbactam in different countries from 2018 to 2022

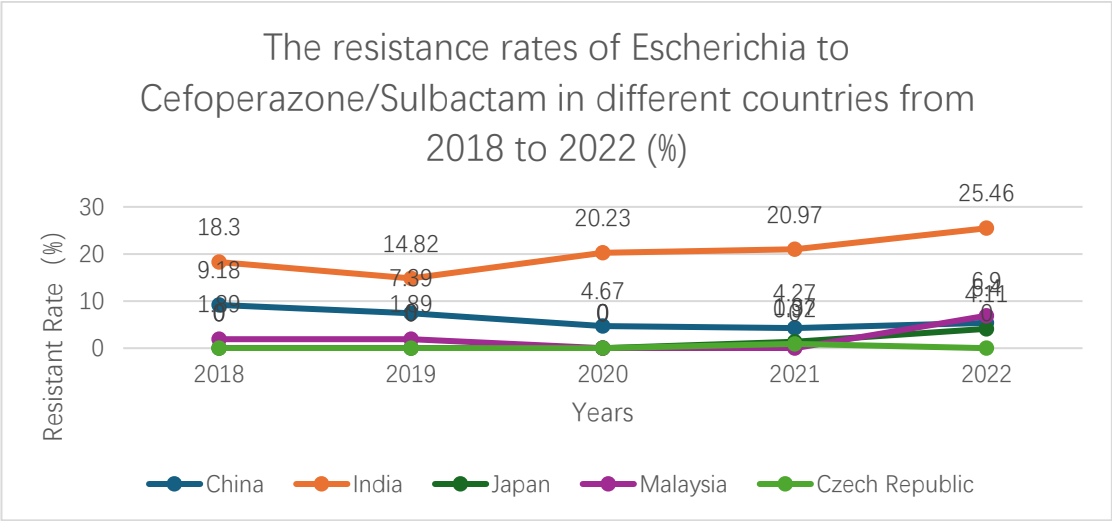

Figure 3 The resistance rates of Escherichia to Cefoperazone/Sulbactam in different countries from 2018 to 2022

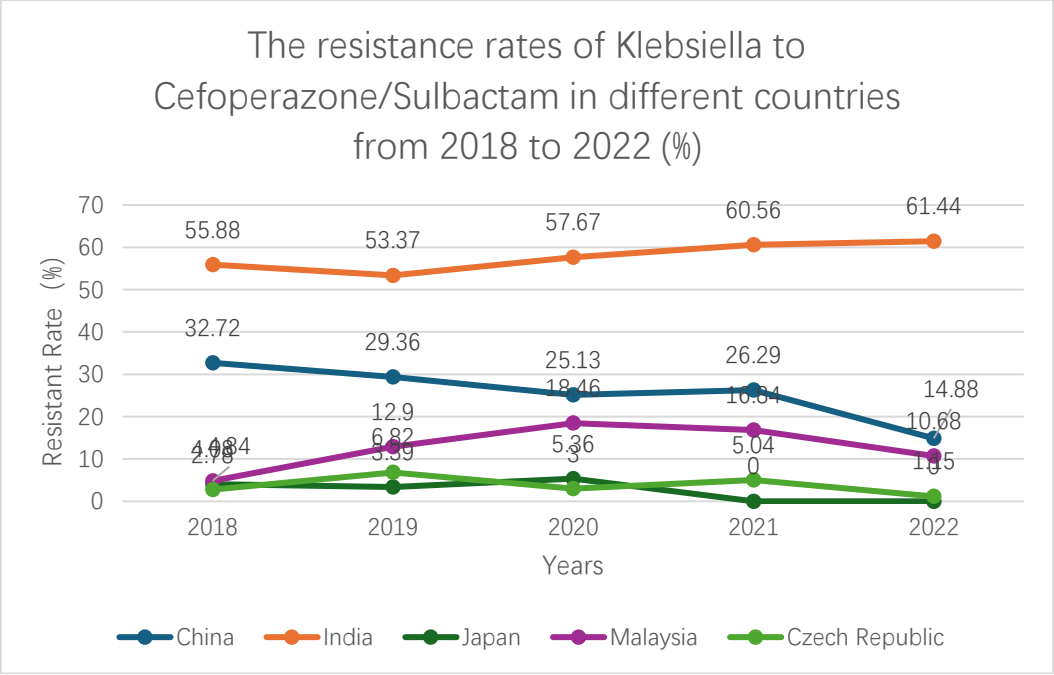

Figure 4 The resistance rates of Klebsiella to Cefoperazone/Sulbactam in different countries from 2018 to 2022

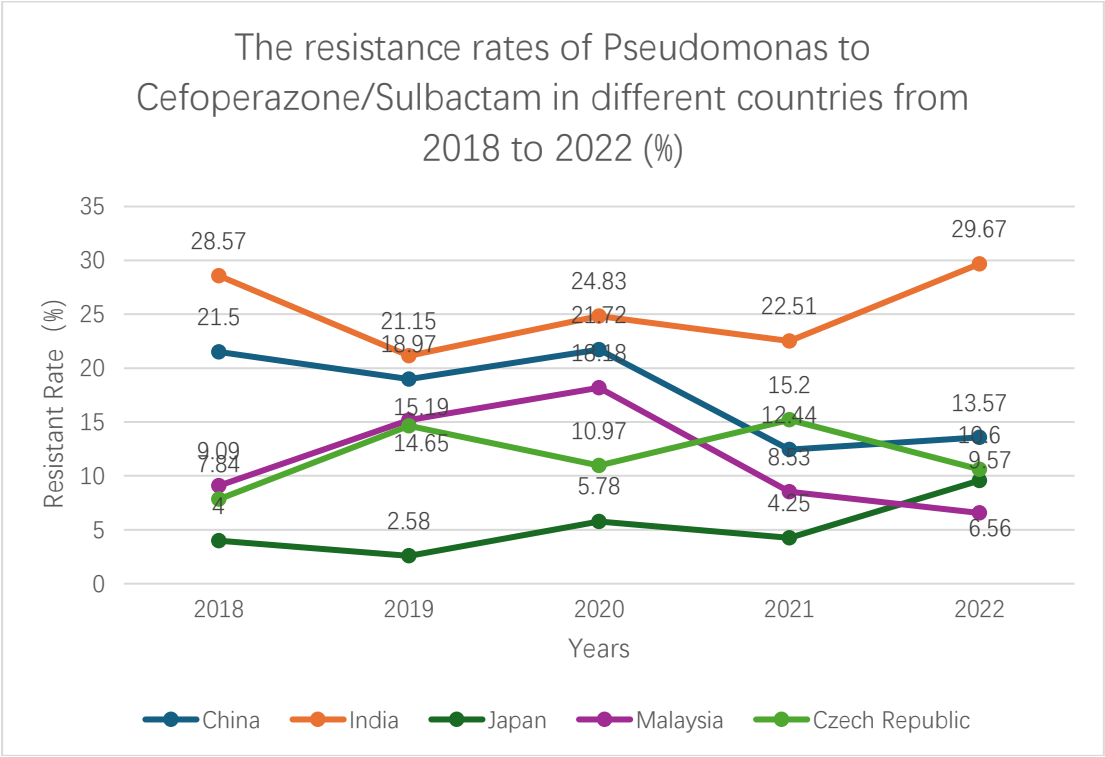

Figure 5 The resistance rates of Pseudomonas to Cefoperazone/Sulbactam in different countries from 2018 to 2022

3.Resistance Mechanisms:

β-Lactamase Inhibitor: Cefoperazone/Sulbactam is an effective β-lactamase inhibitor combination, with Sulbactam enhancing the antibacterial activity of Cefoperazone. While some pathogens may develop resistance,

the combination effectively reduces resistance through β-lactamase inhibition.

In summary, Cefoperazone/Sulbactam demonstrates stable resistance profiles and remains a crucial antibiotic for various bacterial infections. Its effectiveness is supported by usage data and treatment guidelines in several countries. The evidence presented here with respect to resistance and treatment guidelines in countries where the product is currently available, we are applying for the proposal that Cefoperazone/Sulbactam meets and is included in the AWaRe Watch category.

Section 6: Information supporting public health relevance of Cefoperazone/Sulbactam

1.Indication(s) and target population(s)

Cefoperazone/Sulbactam is a broad-spectrum antibiotic recommended for the treatment of various common Gram-negative bacterial infections, including those caused by Enterobacteriaceae, Acinetobacter baumannii, and Pseudomonas aeruginosa. The target population includes patients suffering from these infections, including adults, children, newborns, and the elderly.

2.An alternative medicine currently included in the "Watch" category for the proposed indication(s) is Piperacillin/Tazobactam. However, Cefoperazone/Sulbactam has a broader range of indications, including meningitis and upper respiratory tract infections, which are not covered by Piperacillin/Tazobactam. There are differences in clinical applications, efficacy and safety, drug interactions, and renal function impacts between the two drugs.

6.1 Evidence of the use of Cefoperazone/Sulbactam in the treatment of ESBL

Objective: To summarize the articles on the Epidemiological data on the global disease burden for Gram-negative bacteria (including *E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, A. baumannii, S. maltophilia*), including data specific to WHO regions and country income settings

Literature Search Methodology: A literature search was performed using Google Scholar for the key words' 'epidemiology', 'global disease burden', 'gram negative bacteria', and '*E. coli, K. pneumoniae, P. mirabilis, P. aeruginosa, A. baumannii, S. maltophilia* infection', for articles published from 2017 to 2024. The Google Scholar search yielded a total of 02 relevant articles of which are summarized below:

Nagavi et al (m., N.2022) conducted a systemic analysis to determine the estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with bacterial AMR for 23 pathogens and 88 pathogen–drug combinations in 204 countries and territories in 2019. Data was obtained from systematic literature reviews, hospital systems, surveillance systems, and other sources, covering 471 million individual records or isolates and 7585 study-location-years. There were an estimated 4·95 million (3·62–6·57) deaths associated with bacterial AMR in 2019, including 1·27 million (95% UI 0·911–1·71) deaths attributable to bacterial AMR. At the regional level, we estimated the all-age death rate attributable to resistance to be highest in western sub-Saharan Africa, at 27·3 deaths per

100 000 (20·9–35·3), and lowest in Australasia, at 6·5 deaths (4·3–9·4) per 100 000. Lower respiratory infections accounted for more than 1·5 million deaths associated with resistance in 2019, making it the most burdensome infectious syndrome. Six leading pathogens for deaths associated with resistance (*Escherichia coli,* followed by *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter*

baumannii, and *Pseudomonas aeruginosa*) were responsible for 929 000 (660 000–1 270 000) deaths attributable to AMR and 3·57 million (2·62–4·78) deaths associated with AMR in 2019. One pathogen–drug combination, methicillin resistant *S. aureus*, caused more than 100 000 deaths attributable to AMR in 2019, while six more each caused 50 000–100 000 deaths: multidrug-resistant excluding extensively drug-resistant tuberculosis, third-generation cephalosporin-resistant *E. coli*, carbapenem-resistant *A. baumannii*, fluoroquinolone-resistant *E. coli*, carbapenem-resistant *K. pneumoniae*, and third-generation cephalosporin-resistant *K. pneumoniae*. On the basis of the study results, the authors concluded that AMR is a leading cause of death around the world, with the highest burdens in low-resource settings. Understanding the burden of AMR and the leading pathogen–drug combinations contributing to it is crucial to making informed and location-specific policy decisions, particularly about infection prevention and control programmes, access to essential antibiotics, and research and development of new vaccines and antibiotics.

A review article by Oliverera J and Reygaert WC (Oliveira J,2024), reviews the evaluation of gram-negative bacteria and the interprofessional team's role in managing patients with this condition. Gram-negative bacteria (GNB) are among the world's most significant public health problems due to their high resistance to antibiotics. Enterobacteriaceae and the non-fermenters, are responsible for most clinical isolates; nevertheless, other clinically concerning gram-negative organisms exist, including but not limited to *Neisseria, Haemophilus spp., Helicobacter pylori, and Chlamydia trachomatis*. Multiresistant gram-negative infections (MDRs) are today one of the most significant health challenges in the world due to the inadequate response of these pathogens to antimicrobials, which have practically pulverized by the production of ESBL and carbapenemases. A little over twenty years ago, the first KPC carbapenemase was reported in the United States, and since then, such infections have spread globally. However, since the 1980s, there have been reports of gram-negative strains of ESBL, especially in the hospital environment. According to the Centers for Disease Control and Prevention (CDC), multiresistant gram-negative bacteria are rampant in the United States except in Maine and Idaho. Still, in the US, Livorsi et al. found a variation in the incidence from 0.3 to 2.93 infections per 100000 person-years. Outside the United States, there are already reports of multiresistant bacteria on almost every continent. In Europe, for example, about 25000 people die each year from multidrug-resistant (MDR) infections. Studies show that 12% of E. coli isolates in the USA produce ESBL, while in Latin America and Asia, this percentage may reach 27% and 38%, respectively. Carbapenemases (KPC, NDM-1, IMP, VIM, OXA-48) are characteristically enzymes that hydrolyze carbapenem and most other beta-lactams. In the United States, the most commonly detected are KPC, NDM, and OXA-48; in Europe, the most prevalent are OXA-48, KPC, and VIM, and the NDM are less incident

6.2 Evidence of the use of Cefoperazone/Sulbactam in the treatment of neonatal sepsis

A study aimed to describe antibiotic usage patterns, pathogens, and clinical outcomes in hospitalized neonates with sepsis in low- and middle-income countries. Data were collected from 19 sites across 11 countries from 2018 to 2020. A total of 3,204 infants were enrolled, with a median birth weight of 2,500 g (IQR 1,400 to 3,000) and a postnatal age of 5 days (IQR 1 to 15). Among them, 206 different empiric antibiotic combinations were used for 3,141 infants, categorized into 5 groups based on the World Health Organization (WHO) AWaRe classification. Although Cefoperazone/Sulbactam was not included in any of the five WHO AWaRe groups, the authors noted its recognition and usage in many countries. An “Other” group (n = 204) included less commonly used local regimens not on the WHO Essential Medicines List for children (EMLc), or regimens without a new antibiotic "stem" defining Groups 1 to 5 (e.g., aminoglycosides or glycopeptides used alone or in combination). Cefoperazone/Sulbactam (n = 99) was the most common antibiotic in this category but was used as an initial regimen only in India (n = 86; 14.5%), China (n = 11; 1.9%), and Vietnam (n = 2; 1.0%).

Section 7: Treatment details

Dosage Regimen and Duration of Treatment for Cefoperazone/Sulbactam

2:1 Formulation (1.5 g: Cefoperazone 1 g and Sulbactam 0.5 g):

Adult use:

- Recommended Dose: Administer the dose divided equally every 12 hours.
- For Severe or Difficult-to-Treat Infections: The daily dose can be increased to 12 g (2:1 Cefoperazone/Sulbactam, i.e., Cefoperazone 8 g, Sulbactam 4 g).
- Maximum Daily Dose for Sulbactam: 4 g.

Pediatric use:

- Recommended Dose: 30-60 mg/kg daily, divided into equal doses and administered every 6 to 12 hours.
- For Severe or Difficult-to-Treat Infections: The dose can be increased to 240 mg/kg daily of the 2:1 ratio (160 mg/kg/day cefoperazone activity), divided equally and administered 2 to 4 times per day.

Neonatal use:

- For the First Week of Life: Administer every 12 hours. The maximum daily dose of Sulbactam in neonates should not exceed 80 mg/kg per day. For doses of cefoperazone/sulbactam requiring more than 80 mg/kg/day cefoperazone activity, the 2:1 ratio product must be used.

1:1 Formulation (1 g: Cefoperazone 0.5 g and Sulbactam 0.5 g):

Adult use:

- Recommended Dose: Administer the dose divided equally every 12 hours.
- For Severe or Difficult-to-Treat Infections: The daily dose can be increased to 8 g (1:1 Cefoperazone/Sulbactam, i.e., Cefoperazone 4 g). For patients requiring higher doses of Cefoperazone, additional Cefoperazone can be administered separately or a 2:1 ratio Cefoperazone Sodium/Sulbactam Sodium formulation can be used. The dose should be divided equally and administered every 12 hours.
- Maximum Daily Dose for Sulbactam: 4 g.

Pediatric use:

- Recommended Dose: 40-80 mg/kg daily, divided into equal doses and administered every 6 to 12 hours.
- For Severe or Difficult-to-Treat Infections: The dose can be increased to 160 mg/kg daily of the 1:1 ratio, divided equally and administered 2 to 4 times per day.

Neonatal use:

- For the First Week of Life: Administer every 12 hours. The maximum daily dose of Sulbactam in neonates should not exceed 80 mg/kg per day.

Section 8: Review of evidence for benefits and harms

8.1 Clinical Development and Regulatory History

Cefoperazone/Sulbactam received initial regulatory approval in Japan on 30 April 1986. Cefoperazone/Sulbactam (Superazon in 1:1 or 1:2 ratios) is currently marketed by Pfizer, in 7 countries, in Europe, Asia, and Africa. Furthermore, generic Cefoperazone/Sulbactam is available from other pharmaceutical companies in many countries. The active components of Cefoperazone/Sulbactam are also individually approved worldwide in several countries.

Clinical trials supporting the initial regulatory approvals for Cefoperazone/Sulbactam were conducted in the US and Japan, per standards of the time. Since the initial marketing authorization was obtained, extensive clinical experience has been gained and both the efficacy and safety profiles of Cefoperazone/Sulbactam have been very well established. Included in this clinical overview are summaries of more recent post-marketing clinical trials conducted by the sponsor and summaries of published studies investigating the efficacy and safety of Cefoperazone/Sulbactam.

8.2 RWE (Effectiveness and Safety) Data

A meta-analysis of a hundred publications indicates that Cefoperazone/Sulbactam, widely used as a first-line drug for the treatment of clinical infections, demonstrates good efficacy and safety. Compared to other control drugs, Cefoperazone/Sulbactam shows favorable effectiveness and safety in treating clinical infections.

Title: A systematic review and meta-analysis on the effectiveness and safety of intravenous Cefoperazone/Sulbactam (trade name: Sulperazone) for treating clinical infections in China. (*Chen yuancheng, et al. 2022*)

Researchers collected literaturein the databases of Wan Fang, CNKI, VIP, Sino Med, PubMed, and Cochrane Library） published from 1994 to 2019 regarding the use of Cefoperazone/Sulbactam for treating clinical infections in China and screened them based on inclusion and exclusion criteria. Eventually, 110 articles were included, with 82 and 87 articles included in the meta-analyses for efficacy rate and cure rate, respectively.

The results show that:

- **The overall efficacy rate** of Cefoperazone/Sulbactam for treating clinical infections ： **80.3%** (95% confidence interval: 77.4% to 83.0%).
- **The cure rate ： 50.1%** (95% confidence interval: 45.1% to 55.1%).
- **The bacterial eradication rate ： 81.1%** (95% confidence interval: 76.9% to 84.9%).
- **The incidence rate of adverse events： 7.4%** (95% confidence interval: 6.1% to 8.9%), including adverse events related to the blood system, gastrointestinal tract, liver and kidney function, and skin.

- Safety and efficacy comparison: Compared with other control medications, Cefoperazone/Sulbactam demonstrates good effectiveness and safety in treating clinical infections.

8.3 Cefoperazone/Sulbactam recommendation status in guidelines in various countries

Based on 23 international guidelines, including those from China, Russia and India, Cefoperazone/Sulbactam is recommended as follows:

- Respiratory Infections: For hospital-acquired pneumonia, community-acquired pneumonia, COPD exacerbations, stroke-associated pneumonia, pediatric pneumonia, and severe pneumonia. (Pulmonary Infection Assembly of Chinese Thoracic Society,et al.2018) (Chinese Thoracic Society,et al.2016) (Chinese Society of Emergency Medicine,et al.2023) (Writing Group for the Consensus on Anti-Infective Therapy for Acute Exacerbation of Chronic Obstructive Pulmonary Disease,et al.2019) (Stroke-Associated Pneumonia Diagnosis and Treatment Expert Consensus Group in China,et al.2010) (National Health Commission of the People's Republic of China,et al.2019) (Chinese Pediatric Allergy Specialist Committee of the China Maternal and Child Health Association,et al.2023)
- Intra-abdominal Infections: For cholangitis, post-cholecystectomy cholangitis, and intra-abdominal infections. In India, it is preferred with Piperacillin/Tazobactam for empirical treatment of Gram-negative infections, with carbapenems as an alternative. (Chinese Society of Surgical Infection and Intensive Care,et al.2020) (Chinese Society of Surgery of Chinese Medical Association,et al.2021) (National Clinical Research Center for Children's Health &Diseases,et al.2022)
- Acute Biliary Tract Infections: Effective for both mild to moderate and severe infections. (Study Group of Biliary Tract Surgery in Chinese Society of Surgery of Chinese Medical Association,et al.2019) (Branch of Biliary Surgery, Chinese Society of Surgery, Chinese Medical Association., et al.2021)
- β-Lactamase Inhibitor Guidelines: Recommended for various infection types in combination therapies. (Writing Group for β-Lactamase Inhibitor Guidelines,et al.2020)
- China: Common Gram-negative Bacteria: Recommended for Pseudomonas aeruginosa, Acinetobacter baumannii, Stenotrophomonas maltophilia, and ESBL-producing Enterobacteriaceae. (Pulmonary Infection Assembly of Chinese Thoracic Society,et al.2022) (Chen Baiyi, et al.2012) (Zhou hua, et al.2013) (Writing Group for emergency Diagnosis and Treatment Consensus by Chinese Experts on Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae,et al.2020)
- Russia: Used as first-line therapy for ESBL (-) strains and as second-line for ESBL (+) strains in combination with other antibiotics. (The SCAT program (Strategy for Controlling Antimicrobial Therapy) in inpatient medical care: Russian Clinical Guidelines (2018)) (Diagnosis and Antimicrobial Therapy of

Infections Caused by Multidrug-Resistant Microorganisms, 2022) (Recommendations for Cystic Fibrosis,2021)

- India: Recommended alongside Piperacillin/Tazobactam for empirical treatment of Gram-negative bacterial infections, including ESBL-producing bacteria, with carbapenems as an alternative. (Research, 2019)

Overall Conclusion: Cefoperazone/Sulbactam is widely recommended across various infection types and regions, highlighting its significant role in infection management. These guidelines provide valuable references for clinicians, affirming its support from high-quality international recommendations.

8.4 RWE Data in treating ESBL+ bacterial infection

Cefoperazone/sulbactam is used for the treatment of ESBL-producing bacteria. Below are articles published internationally on the treatment of EMBL bacteria with cefoperazone/sulbactam.

- Bakthavatchalam et al (Bakthavatchalam YD, 2024) conducted a study to evaluate the effect of CPZ/SUL on ESBL producing Enterobactales. Non-duplicate contemporary ESBL and/or OXA-1 expressing E. coli (n = 117) and K. pneumoniae (n = 71) isolates were included in this study. The MIC of cefepime/sulbactam and its comparators were determined using a broth microdilution method. The presence of ESBL and OXA-1 genes were identified using multiplex polymerase chain reaction (PCR). The combination of CPZ/SUL inhibited 89% of the ESBL-E. coli isolates. Additionally, an improvement in the susceptibility of ESBL-K. pneumoniae (91%) and OXA-1 expressing K. pneumoniae (81%) isolates to cefoperazone was observed with sulbactam concentrations of 8 mg/L. On the basis of the study results, the authors concluded that adding a higher sulbactam concentration enhances cefepime's activity against contemporary ESBL/OXA-1 expressing Enterobacterales.
- Su et al (Su J, 2018) conduced a retrospective cohort study to evaluate and compare the clinical efficacy of CPZ/SUL with that of a carbapenem in the treatment of bloodstream infections (BSIs) caused by ESBL-producing Enterobacteriaceae. Patients with monomicrobial ESBL-producing Enterobacteriaceae BSIs empirically treated with CPZ/SUL or a carbapenem were included. Outcomes of interest were clinical response and 14-day mortality. To make a comparison of the efficacy of CPZ/SUL and a carbapenem more accurate, propensity score analysis was performed. Success rates or 14-day mortality were not statistically significant between CPZ/SUL (n = 17) and carbapenem (n = 46) groups. In the propensity score analysis with 17 case–control pairs, a lower success rate was observed in the CPZ/SUL group (70.6%, 12/17) compared to the carbapenem group (94.1%, 16/17), but the difference was not significant (P = 0.175). Also, the sepsis-related mortality and the 14-day mortality rates did not show any significant

difference (P = 1.000 for both). Within 14 days, death was observed in 66.7% (2/3) patients with a Pitt bacteremia score ≥5 in the CPZ/SUL group; however, none (0/14) of the patients with a Pitt bacteremia score <5 died within 14 days (P = 0.022). On the basis of the study results, the authors concluded that CPZ/SUL had a lower success rate, and a higher 14-day mortality rate compared with carbapenems, although the differences were not statistically significant because of the small patient numbers.

- Naz et al (Naz Q, 2017) conducted an observational study to evaluate the antimicrobial susceptibility pattern of Piperacillin/Tazobactam (Pip/Tazo) and Cefoperazone/Sulbactam (Cefoperazone/Sulbactam) against isolates of Enterobacteriaceae from various clinical samples of inpatients and outpatients. A total of 2111 clinical samples were received for culture and sensitivity from both in and outpatients. In Enterobacteriaceae 47% isolates were found as ESBL producers while 53% were found to be non ESBLs producing organisms. Samples were inoculated on Chocolate agar, Sheep blood agar and MacConkey's agar and were incubated for 24 to 48 hours according to standard technique. All isolates belonging to the family Enterobacteriaceae identified by conventional biochemical tests were included in the study. Antimicrobial sensitivities of Enterobacteriaceae were tested and interpreted by Kirby-Bauer disc diffusion method according to Clinical Laboratory Standard Institution (CLSI) criteria. In total, including all isolates of Enterobacteriaceae the antimicrobial sensitivity is 80% (172/214) for Pip/Tazo and 83% (178/214) for Cefoperazone/Sulbactam. On the basis of the study results, the authors concluded that Pip/Tazo and Cefoperazone/Sulbactam are potential and better empirical treatment options for treating isolates of Enterobacteriaceae. This will help in reducing selection pressure on last resort antimicrobials and hence curtail antimicrobial resistance.
- Kadry et al (Kadry AA, 2022) conducted an in vitro study to assess the activity of classical and novel combinations of BLBLI against E. coli clinical isolates. A total of 140 clinical isolates of E. coli were collected from clinical specimens from Gastrointestinal Surgery Center (GISC) in Egypt. The ESBL was detected by double disk synergy test and the MICs were determined using broth microdilution method. About 89.2% of the E. coli isolates were susceptible to CPZ/SUL. After using new BLBLI, the isolate restored the susceptibility with CPZ/SUL (16 µg/mL). Additionally, CPZ/SUL exhibited the lowest P-value (0.0001) after applying the one-way ANOVA test. The CPZ/SUL combination was synergistic in 63% (58/92) and partially synergistic in 21% (19/92). On the basis of the study results, the authors concluded that BLBLI combinations were totally effective against most E. coli clinical isolates and the MIC values were greatly declined. Also, the antibacterial activity of some antimicrobial agents can be enhanced by the addition of new □-lactamase inhibitors.

8.5 The recommended status of Cefoperazone/Sulbactam in the treatment of ESBL-producing bacterial

infections in various national guidelines

Below are the recommendations on the role of Cefoperazone/Sulbactam in the treatment of ESBL-producing bacteria from various national guidelines. These guidelines consist of 4 Chinese guidelines, 1 Indian guideline, and 1 Russian guideline. In 2023 China, India, and Russia accounted for 88% of the total global volume of Cefoperazone/Sulbactam.（Source: IQVIA 2023FY by volume）

China Guidelines (4 guidelines):

- Clinical Guidelines for the Use of Antibacterial Agents in Febrile Neutropenic Patients (2020, China) (Chinese Society of Hematology et. Al. 2020)

  For FN patients requiring adjustment of antimicrobial therapy, Cefoperazone/Sulbactam is recommended as one of the first-line drugs for treating ESBL-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Burkholderia ce*pacia complex infections.

- Guidelines for the Diagnosis and Treatment of Community-Acquired Pneumonia in Adults (2016, China) (Chinese Thoracic Society,et al.2016)

  Cefoperazone/Sulbactam is used for the infection of Pseudomonas aeruginosa, ESBL-producing Enterobacteriaceae, or Acinetobacter species.

  Expert Consensus on the Clinical Application of β-Lactam/β-Lactamase Inhibitor Combination Agents (2020, China)

  (Writing Group for β-Lactamase Inhibitor Guidelines: Recommended for various infection types in combination therapies, et al.2020)

- Cefoperazone/Sulbactam or other monotherapy options can be considered, especially if there is a risk of ESBL-producing bacteria infection.

- Emergency Diagnosis and Treatment Consensus by Chinese Experts on Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae.(2020, China)(Writing Group for emergency Diagnosis and Treatment Consensus by Chinese Experts on Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae, et al. 2020)

  Cefoperazone/Sulbactam is recommended for mild to moderate infections caused by ESBL-producing Enterobacteriaceae, with a standard dose of 3g/q12-8h.

CEFOPERAZONE/SULBACTAM Russia

Guidelines (SCAT Program, 2018):

- First-line therapy: Cefoperazone/Sulbactam is recommended for ESBL-negative strains of Enterobacterales, based on sensitivity to the antibiotic, which may include CEFOPERAZONE/SULBACTAM.
- Second-line therapy: For ESBL-positive strains of Enterobacterales, CEFOPERAZONE/SULBACTAM can be used in combination with other antibiotics, including carbapenems.

India

Guidelines:

- For empirical treatment of Gram-negative bacterial intra-abdominal infections, CEFOPERAZONE/SULBACTAM and Pip/Tazo are preferred, with carbapenems as an alternative.
- For ESBL-positive bacteria, CEFOPERAZONE/SULBACTAM and Pip/Tazo are preferred, with carbapenems as an alternative.

Summary: China and India recommend CEFOPERAZONE/SULBACTAM and Pip/Tazo for the treatment of ESBL-positive infections, with carbapenems as alternatives for more severe cases, or when other options are not effective. Russia uses CEFOPERAZONE/SULBACTAM as a second-line option for ESBL-positive strains, often in combination with other antibiotics. The recommendation of cefoperazone/sulbactam before the use of carbapenems indicates its advantage as a first-line treatment. It can serve as an alternative to reduce the frequency of carbapenem use, which helps to delay the development of resistance while providing patients with a rapid and effective treatment option. This strategy highlights the important role of cefoperazone/sulbactam in addressing resistant infections.

Section 9: Summary of recommendations in current clinical guidelines

Country	Guidelines	Recommendation
China	**Clinical Guidelines for the Use of Antibacterial Agents in Febrile Neutropenic Patients (2020, China)** (Chinese Society of Hematology,et al.2020)	1. For febrile neutropenic (FN) patients, Cefoperazone/Sulbactam is one of the drugs that can be selected for both escalation and de-escalation therapy. 2. For FN patients requiring adjustment of antimicrobial therapy, Cefoperazone/Sulbactam is recommended as one of the first-line drugs for treating ESBL-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Burkholderia cepacia* complex infections.
China	**Guidelines for Diagnosis and Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia in Adults (2018, China)** (Pulmonary Infection Assembly of Chinese Thoracic Society,et al.2018)	Initial empirical treatment for hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP), Cefoperazone/Sulbactam is recommended as one of the drugs for both low-risk and high-risk MDR bacterial infections.
China	**Guidelines for the Diagnosis and Treatment of Community-Acquired Pneumonia in Adults (2016, China)** (Chinese Thoracic Society,et al.2016)	1**. In empirical treatment** for community-acquired pneumonia (CAP), **Cefoperazone/Sulbactam** may be considered for hospitalized CAP patients aged ≥65 years or with underlying diseases at high risk of ESBL-producing Enterobacteriaceae infection. In cases of CAP with risk factors for Pseudomonas aeruginosa infection or structural lung diseases, Cefoperazone/Sulbactam may be considered. 2. **In targeted therapy** for CAP, **Cefoperazone/Sulbactam** and other drugs may be considered when the pathogens are *Pseudomonas aeruginosa*, ESBL-producing Enterobacteriaceae, or Acinetobacter species.
China	**Chinese Expert Consensus on The Management of Lower Respiratory Tract Infections of Pseudomonas aeruginosa (2022, China)** (Pulmonary Infection Assembly of Chinese Thoracic Society, et al. 2022)	For patients with non-multidrug-resistant Pseudomonas aeruginosa (MDR-PA) with mild lower respiratory tract infections and no significant underlying diseases, monotherapy with antibiotics with anti-Pseudomonas activity, typically anti-Pseudomonas β-lactam antibiotics such as enzyme inhibitor combinations (**Cefoperazone/Sulbactam**, etc.), may be used. In cases of MDR-PA, β-lactam antibiotics may be chosen as one of the options for combination therapy drug selection.
China	**Expert Consensus on Diagnosis, Treatment, and Prevention of Acinetobacter baumannii Infections (2021, China)** (Chen Baiyi, et al.2012)	1. **Cefoperazone/Sulbactam** is one of the first-line treatment options for treating *Acinetobacter baumannii* (AB) infection. 2. For multidrug-resistant *Acinetobacter baumannii* (MDR-AB), **Cefoperazone/Sulbactam**, ampicillin/sulbactam, or carbapenems may be selected based on susceptibility testing. They may be used in combination with aminoglycosides or fluoroquinolones. 3. For extensively drug-resistant AB, combination therapy with two or even three drugs is often employed. **Cefoperazone/Sulbactam** is one of the options for combination therapy drug selection.
China	**Expert Consensus on Diagnosis, Treatment, and Prevention of Burkholderia cepacia Complex Infections (2013, China)** (Zhou hua,et al.2013)	The choice of treatment includes SMZ/TMP, cephalosporin/beta-lactamase inhibitor combination (**Cefoperazone/Sulbactam**, ticarcillin/clavulanic acid), etc. **Cefoperazone/Sulbactam** exhibits good antibacterial activity against *Pseudomonas aeruginosa* in vitro.
China	**Expert Consensus on the Clinical Application of β-Lactam/β-Lactamase Inhibitor Combination Agents (2020, China)** (Writing Group for β-Lactamase Inhibitor Guidelines: Recommended for various infection types in	According to the CHINET surveillance results, the most common Gram-negative bacteria clinically isolated in China are Enterobacteriaceae, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. **Cefoperazone/Sulbactam** is recommended as one of the treatment options for these common Gram-negative bacterial infections. For pneumonia: Patients with risk factors for *Pseudomonas aeruginosa*

	combination therapies, et al.2020)	infection should be treated with a combination of cephalosporin/beta-lactamase inhibitor compounds (such as Cefoperazone/Sulbactam). - In non-severe hospital-acquired pneumonia (HAP) patients, Cefoperazone/Sulbactam is recommended as one of the treatment options. - For ventilator-associated pneumonia (VAP) patients without risk factors for drug-resistant bacteria, cephalosporin/beta-lactamase inhibitor compounds (such as Cefoperazone/Sulbactam) should be used. For abdominal infections: For community-acquired mild to moderate biliary tract infections, Cefoperazone/Sulbactam or other monotherapy options can be considered, especially if there is a risk of ESBL-producing bacteria infection. Cefoperazone/Sulbactam and other drugs are effective for treating complex abdominal infections, including those caused by ESBL-producing bacteria. For bloodstream infections: Empirical coverage of multidrug-resistant Gram-negative bacteria, such as Cefoperazone/Sulbactam, is recommended for sepsis, immunocompromised, and neutropenic patients. For urinary tract infections: Cefoperazone/Sulbactam can be considered for empirical treatment of acute upper urinary tract infections, especially in moderate to severe infections or those with systemic symptoms. It is also recommended for patients with risk factors for *Pseudomonas aeruginosa* infection. In targeted therapy: Cefoperazone/Sulbactam is preferred for the treatment of ESBL-producing Enterobacteriaceae or *Pseudomonas aeruginosa* infections. For Acinetobacter baumannii infections: Compounds containing sulbactam, such as Cefoperazone/Sulbactam, can be considered for the treatment of *A. baumannii* infections. For febrile neutropenia: Cefoperazone/Sulbactam and other cephalosporin/beta-lactamase inhibitor compounds can be administered to patients with mild to moderate infections or those without confirmed colonization of drug-resistant bacteria or previous infections caused by drug-resistant bacteria.
China	**Emergency Diagnosis and Treatment Consensus by Chinese Experts on Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae. (2020, China)**(Writing Group for emergency Diagnosis and Treatment Consensus by Chinese Experts on Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae, et al. 2020)	Cefoperazone/Sulbactam is recommended for mild to moderate infections caused by ESBL-producing Enterobacteriaceae, with a standard dose of 3g/q12-8h.
India	**Treatment Guidelines for Antimicrobial Use in Common Syndromes(2019, India)**(Research, et al.2019)	Cefoperazone/Sulbactam is recommended for: Empiric Therapy for Suspected Gram-Negative Infections (e.g., pyelonephritis or intra-abdominal infections) as initial Treatment(preferred) Sepsis or septic shock with focus unclear(alternative) Community acquired intra-abdominal infection of mild to moderate severity(first choise ABs) Commonly caused by Gram-negative organisms, including *Escherichia coli* and Klebsiella. Occasionally, Staphylococcus, Enterococcus, or Streptococcus may be implicated(first choise ABs)
India	**Guidelines for diagnosis and management of community- and hospital-acquired pneumonia in adults Joint ICSNCCP(I) recommendations (2012, India)**(Gupta D, et al.2012)	For patients in ICU, if P. aeruginosa was considered, antibiotics such as cefepime, ceftazidime, cefoperazone, piperacillin-tazobactam, cefoperazone-sulbactam, imipenem or meropenem were administered. For the treatment of HAP, 2 to 3 g intravenous (IV) infusion of cefoperazone-sulbactam twice a day (BID) or thrice a day (TID) was recommended. For multi-drug resistant (MDR) Acinetobacter infections, carbapenems, polymyxins, tigecycline, and combination therapy with sulbactam or

		rifampicin, or combination of carbapenem with colistin were considered.
India	**National Treatment Guidelines for Antimicrobial Use in Infectious Diseases. (2016, India)**(National Treatment Guidelines for Antimicrobial Use in Infectious Diseases.2016)	Acute osteomyelitis or septic arthritis was treated primarily with IV ceftriaxone (2 g) followed by oral cloxacillin (500 mg) or cephalexin (500 mg). IV piperacillin-tazobactam (4.5 g) or IV cefoperazone-sulbactam (3 gm) and IV clindamycin (600-900 mg) were the alternative treatment options
Russia	**The SCAT program (Strategy for Controlling Antimicrobial Therapy) in inpatient medical care: Russian Clinical Guidelines (2018, Russia)**(SCAT program, et al.2018)	- For first-line therapy of ESBL (Extended spectrum beta-lactamases) (-) strains of Enterobacterales with established sensitivity of the pathogen to the antibiotic; - For second-line therapy of ESBL (Extended spectrum beta-lactamases) (+) strains of Enterobacterales in combination with other antibiotics (carbapenems).
Russia	**Diagnosis and Antimicrobial Therapy of Infections Caused by Multidrug-Resistant Microorganisms" (2022, Russia)**(Diagnosis, et al.2022)	Therapy of *A. baumannii* in combination with other antibiotics (Tigecycline), as decided by the expert committee (since only high off-label doses of the drug are effective).
Russia	**Recommendations for Cystic Fibrosis (2021,Russia)**(Recommendations for Cystic Fibrosis, et al.2021)	In patients with cystic fibrosis, when *P. aeruginosa* is isolated from sputum/bronchial secretions as part of combined therapy

Section 10: Summary of available data on comparative cost and cost-effectiveness

Two articles will be included here: one from China and one from India.

China

A Chinese study reports that with equivalent efficacy, the cost of Cefoperazone/Sulbactam is approximately 1/3 to 1/2 of the cost of Piperacillin/Tazobactam and Imipenem/Cilastatin. (Tang kejing, et al.2017)

India

An Indian study (in English) highlights that Cefoperazone/Sulbactam had a lower drug cost per patient and a lower overall average cost of treatment per patient compared to the comparator drugs. (Kochhar P, 2008)

Section 11: Regulatory status, market availability and pharmacopoeial standards

Cefoperazone/Sulbactam is not included in the U.S. Pharmacopeia (USP) because the combination has not been marketed in the United States. However, the individual components, cefoperazone and sulbactam, are each listed in the USP, as well as in the European Pharmacopoeia (EP) and British Pharmacopoeia (BP). Please refer to the table below for further details.

Table 1. Cefoperazone sodium

Parameter	**United States Pharmacopoeia (USP-NF) (Cefoperazone sodium Sodium USP NF 2023 Issue.)**	**European Pharmacopoeia (Ph Eur) (Cefoperazone Sodium, E P 11.6)**	**British Pharmacopoeia (Cefoperazone sodium BP 2024 (EP 11.5 update))**
Molecular formula Molecular weight Definition	$C_{25}H_{26}N_9NaO_8S_2$ 667.65 Cefoperazone Sodium contains the equivalent of NLT 870 µg/mg and NMT 1015 µg/mg of cefoperazone ($C_{25}H_{27}N_9O_8S_2$), calculated on the anhydrous basis.	$C_{25}H_{26}N_9NaO_8S_2$ 668 Sodium (6*R*,7*R*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Semi-synthetic product derived from a fermentation product. *Content*: 95.0 per cent to 102.0 per cent (anhydrous substance).	$C_{25}H_{26}N_9NaO_8S_2$ 668 Sodium (6*R*,7*R*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate. Semi-synthetic product derived from a fermentation product. **Content** 95.0 per cent to 102.0 per cent (anhydrous substance).
IDENTIFICATION	A. The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay. B. Identification Tests—General ⟨191⟩, Chemical Identification Tests, Sodium: Meets the requirements	A. Infrared absorption spectrophotometry (2.2.24). Preparation: dissolve the substance to be examined in methanol R and evaporate to dryness; examine the residue. Comparison: Ph. Eur. reference spectrum of cefoperazone sodium. B. Examine the chromatograms obtained in the assay. Results: the principal peak in the chromatogram obtained with test solution (a) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a). C. It gives reaction (a) of sodium (2.3.1).	A. Infrared absorption spectrophotometry (*2.2.24*). *Preparation* Dissolve the substance to be examined in *methanol R* and evaporate to dryness; examine the residue. *Comparison Ph. Eur. reference spectrum of cefoperazone sodium*. B. Examine the chromatograms obtained in the assay. *Results* The principal peak in the chromatogram obtained with test solution (a) is similar in retention time and size to the principal peak in the chromatogram obtained with reference solution (a). C. It gives reaction (a) of sodium (*2.3.1*).

Parameter	United States Pharmacopoeia (USP-NF) (Cefoperazone sodium Sodium USP NF 2023 Issue.)	European Pharmacopoeia (Ph Eur) (Cefoperazone Sodium, E P 11.6)	British Pharmacopoeia (Cefoperazone sodium BP 2024 (EP 11.5 update))
Assay acceptance criteria	870–1015 µg/mg on the anhydrous basis	Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modifications. *Injection*: test solution (a) and reference solution (a). *System suitability*: reference solution (a): – *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections. Calculate the percentage content of cefoperazone sodium by multiplying the percentage content of cefoperazone by 1.034.	Liquid chromatography (2.2.29) as described in the test for related substances with the following modifications. *Injection* Test solution (a) and reference solution (a). *System suitability* Reference solution (a): — *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections. Calculate the percentage content of *cefoperazone* sodium by multiplying the percentage content of *cefoperazone* by 1.034.
pH	4.5–6.5	4.5 to 6.5	4.5 to 6.5.
Impurities	Not given	A. (5a*R*,6*R*)-6-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)-carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione, B. (6*R*,7*R*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)-carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[(4-methyl-5-thioxo-4,5-dihydro-1*H*-tetrazol-1-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, C. 1-methyl-1*H*-tetrazole-5-thiol, D. (6*R*,7*R*)-7-amino-8-oxo-3-[(1*H*-1,2,3-triazol-4-ylsulfanyl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-TACA), E. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA), F. (6*R*,7*S*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazine-1-yl)-carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.	A. (5a*R*,6*R*)-6-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-5a,6-dihydro-3*H*,7*H*-azeto[2,1-*b*]furo[3,4-*d*][1,3]thiazine-1,7(4*H*)-dione, B. (6*R*,7*R*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazin-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[(4-methyl-5-thioxo-4,5-dihydro-1*H*-tetrazol-1-yl)methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, C. 1-methyl-1*H*-tetrazole-5-thiol, D. (6*R*,7*R*)-7-amino-8-oxo-3-[(1*H*-1,2,3-triazol-4-ylsulfanyl)methyl]-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-TACA), E. (6*R*,7*R*)-3-[(acetyloxy)methyl]-7-amino-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid (7-ACA), F. (6*R*,7*S*)-7-[[(2*R*)-2-[[(4-ethyl-2,3-dioxopiperazine-1-yl)carbonyl]amino]-2-(4-hydroxyphenyl)acetyl]amino]-3-[[(1-methyl-1*H*-tetrazol-5-yl)sulfanyl]methyl]-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid.

Table 2. Sulbactam sodium

Parameter	United States Pharmacopoeia (USP-NF) (Sulbactam Sodium USP NF 2023 Issue.)	European Pharmacopoeia (Ph Eur) (Sulbactam Sodium, EUROPEAN PHARMACOPOEIA 11.6)	British Pharmacopoeia (Sulbactam sodium BP 2024 (Ph. Eur. 11.5 update))
Molecular formula Molecular weight Definition	$C_8H_{10}NNaO_5S$ 255.22 Sulbactam Sodium contains NLT 886 and NMT 941 µg/mg of sulbactam ($C_8H_{11}NO_5S$), calculated on the anhydrous basis.	C8H10NNaO5S 255.2 Sodium (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide. Semi-synthetic product derived from a fermentation product. *Content*: 97.0 per cent to 102.0 per cent (anhydrous substance).	$C_8H_{10}NNaO_5S$ 255.2 Sodium (2*S*,5*R*)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide. Semi-synthetic product derived from a fermentation product.
IDENTIFICATION	▲•A. Spectroscopic Identification Tests ⟨197⟩, Infrared Spectroscopy:197K▲ (USP 1-Dec-2023) Change to read: •▲B.▲ (USP 1-Dec-2023)The retention time of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay. Change to read: •▲C.▲ (USP 1-Dec-2023) Identification Tests—General ⟨191⟩, Chemical Identification Tests, Sodium:Meets the requirements	A. Infrared absorption spectrophotometry (2.2.24). Comparison: sulbactam sodium CRS. B. It gives reaction (a) of sodium (2.3.1).	A. Infrared absorption spectrophotometry (*2.2.24*). *Comparison sulbactam sodium C RS*. B. It gives reaction (a) of sodium (*2.3.1*).
Assay acceptance criteria	**Acceptance criteria:** 886–941 µg/mg on the anhydrous basis	Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification. *Injection*: test solution and reference solution (a). *System suitability*: reference solution (a): – *symmetry factor*: maximum 3.0 for the peak due to sulbactam. Calculate the percentage content of C8H10NNaO5S taking into account the assigned content of *sulbactam CRS* and a conversion factor of 1.094.	Liquid chromatography (*2.2.29*) as described in the test for related substances with the following modification. *Injection* Test solution and reference solution (a). Calculate the percentage content of $C_8H_{10}NNaO_5S$ taking into account the assigned content of *sulbactam CRS* and a conversion factor of 1.094.
pH		4.5 to 7.2; if the substance is sterile: 5.2 to 7.2.	4.5 to 7.2; if the substance is sterile: 5.2 to 7.2.

Table 2. Sulbactam sodium

Parameter	United States Pharmacopoeia (USP-NF) (Sulbactam Sodium USP NF 2023 Issue.)	European Pharmacopoeia (Ph Eur) (Sulbactam Sodium, EUROPEAN PHARMACOPOEIA 11.6)	British Pharmacopoeia (Sulbactam sodium BP 2024 (Ph. Eur. 11.5 update))
Impurities	a 3-Sulfino-d-valine; (2S)-2-Amino-3-methyl-3-sulfinobutanoic acid. b ▲▲ (USP 1-Dec-2023)(2S,5R,6R)-6-Amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. c (2S,5R,6R)-6-Bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide. d 6-Bromopenicillanic acid; (2S,5R,6R)-6-Bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. e 6,6-Dibromopenicillanic acid sulfone; also known as (2S,5R)-6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide. f 6,6-Dibromopenicillanic acid; also known as (2S,5R)-6,6-Dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.	A. (2*S*)-2-amino-3-methyl-3-sulfinobutanoic acid, B. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid), C. (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6-bromopenicillanic acid sulfone), D. (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-bromopenicillanic acid), E. (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6,6-dibromopenicillanic acid sulfone), F. (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6,6-dibromopenicillanic acid), G. (2*S*)-2-[[(2*E*)-2-carboxyethenyl]amino]-3-methyl-3-sulfinobutanoic acid.	A. (2*S*)-2-amino-3-methyl-3-sulfinobutanoic acid, B. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid), C. (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6-bromopenicillanic acid sulfone), D. (2*S*,5*R*,6*R*)-6-bromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-bromopenicillanic acid), E. (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid 4,4-dioxide (6,6-dibromopenicillanic acid sulfone), F. (2*S*,5*R*)-6,6-dibromo-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6,6-dibromopenicillanic acid), G. (2*S*)-2-[[(2*E*)-2-carboxyethenyl]amino]-3-methyl-3-sulfinobutanoic acid.

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