SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Ampicillin Sodium and Sulbactam Sodium for Injection 0.75 g

2. Qualitative and quantitative composition

Each vial contains Ampicillin (as sodium salt) equivalent to 0.5 g and Sulbactam (as sodium salt) equivalent to 0.25 g.

Excipient with known effect

Each vial of Ampicillin Sodium and Sulbactam Sodium for Injection 0.5 g / 0.25 g contains approximately57.5 mg of sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder for solution for injection/ infusion.

White or almost white powder or crystalline powder.

4. Clinical particulars

4.1 Therapeutic indications

Ampicillin and Sulbactam for Injection is indicated for the treatment of infections due to susceptible strains of the designated microorganisms in the conditions listed below.

Skin and Skin Structure Infections caused by beta-lactamase producing strains of Staphylococcus aureus, Escherichia coli,* Klebsiella spp.* (including K. pneumoniae*), Proteus mirabilis,* Bacteroidesfragilis,* Enterobacter spp.,* and Acinetobactercalcoaceticus.*

NOTE: For information on use in pediatric patients (see **PRECAUTIONS–Pediatric Use**and **CLINICAL STUDIES** sections).

Intra-Abdominal Infections caused by beta-lactamase producing strains of Escherichia coli, Klebsiella spp. (including K. pneumoniae*), Bacteroides spp. (including B. fragilis), and Enterobacter spp.*

Gynecological Infections caused by beta-lactamase producing strains of Escherichia coli,* and Bacteroides spp.* (including B. fragilis*).

While ampicillin and sulbactam for injection is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to treatment with ampicillin and sulbactam for injection due to its ampicillin content. Therefore, mixed infections caused by ampicillin-susceptible organisms and beta-lactamase producing organisms susceptible to ampicillin and sulbactam for injection should not require the addition of another antibacterial.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify the organisms causing infection and to determine their susceptibility to the drug product.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies when there is reason to believe the infection may involve any of the beta-lactamase producing organisms listed above in the indicated organ systems. Once the results are known, therapy should be adjusted if appropriate.

To reduce the development of drug-resistant bacteria and maintain effectiveness of Ampicillin and Sulbactam for injection and other antibacterial drugs, Ampicillin and Sulbactam for injection should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

* Efficacy for this organism in this organ system was studied in fewer than 10 infections.

4.2 Posology and method of administration

Ampicillin and Sulbactam for injection may be administered by either the IV or the IM routes.

For IV administration, the dose can be given by slow intravenous injection over at least 10–15 minutes or can also be delivered in greater dilutions with 50–100 mL of a compatible diluent as an intravenous infusion over 15–30 minutes.

Ampicillin and Sulbactam for injection may be administered by deep intramuscular injection.

The recommended adult dosage of this product is 1.5 g (1 g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt) to 3 g (2 g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) every six hours. This 1.5 to 3 g range represents the total of ampicillin content plus the sulbactam content, and corresponds to a range of 1 g ampicillin/0.5 g sulbactam to 2 g ampicillin/1 g sulbactam. The total dose of sulbactam should not exceed 4 grams per day.

Pediatric Patients 1 Year of Age or Older:

The recommended daily dose in pediatric patients is 300 mg per kg of body weight administered via intravenous infusion in equally divided doses every 6 hours. This 300 mg/kg/day dosage represents the total ampicillin content plus the sulbactam content, and corresponds to 200 mg ampicillin/100 mg sulbactam per kg per day. The safety and efficacy of the drug product administered via intramuscular injection in pediatric patients have not been established. Pediatric patients weighing 40 kg or more should be dosed according to adult recommendations, and the total dose of sulbactam should not exceed 4 grams per day. The course of intravenous therapy

should not routinely exceed 14 days. In clinical trials, most children received a course of oral antimicrobials following initial treatment with intravenous route.

Impaired Renal Function

In patients with impairment of renal function the elimination kinetics of ampicillin and sulbactam are similarly affected, hence the ratio of one to the other will remain constant whatever the renal function. The dose in such patients should be administered less frequently in accordance with the usual practice for ampicillin and according to the following recommendations:

Table 1 Dosage Guide for Patients with Renal Impairment

Creatinine Clearance (mL/min/1.73m2)	**Ampicil in/Sulbactam Half-Life (Hours)**	**Recommended Dosage**
≥30	1	1.5–3 g q 6h–q 8h
15–29	5	1.5–3 g q 12h
5–14	9	1.5–3 g q 24h

When only serum creatinine is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$Males\ \frac{\text{Weight(Kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

Females 0.85×above value

4.3 Contraindications

The use of Ampicillin and Sulbactam for injection is contraindicated in individuals with a history of serious hypersensitivity reactions (e.g., anaphylaxis or Stevens-Johnson syndrome) to ampicillin, sulbactam or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins).

Ampicillin and Sulbactam for injection is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with this drug product.

4.4 Special warnings and precautions for use

WARNINGS

Hypersensitivity

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or hypersensitivity reactions to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated

with cephalosporins. Before therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, it should be discontinued and the appropriate therapy instituted.

Hepatotoxicity

Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of this product. Hepatic toxicity is usually reversible; however, deaths have been reported. Hepatic function should be monitored at regular intervals in patients with hepatic impairment.

Severe Cutaneous Adverse Reactions

This product may cause severe skin reactions, such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), dermatitis exfoliative, erythema multiforme, and Acute generalized exanthematouspustulosis (AGEP). If patients develop a skin rash they should be monitored closely and Ampicillin sodiun and Sulbactam sodium for injection discontinued if lesions progress (see CONTRAINDICATIONS and ADVERSE REACTIONS sections).

***Clostridium difficile*-Associated Diarrhea**

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ampicillin and sulbactam for injection, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. difficile.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of C. difficile cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against C. difficile may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of C. difficile, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS

General

A high percentage of patients with mononucleosis who receive ampicillin develop a skin rash. Thus, ampicillin class antibacterial should not be administered to patients with mononucleosis. In patients treated with ampicillin and sulbactam for injection, the possibility of superinfections with mycotic or bacterial pathogens should be kept

in mind during therapy. If superinfections occur (usually involving Pseudomonas or Candida), the drug should be discontinued and/or appropriate therapy instituted.

Prescribing ampicillin and sulbactam for injection in the absence of proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Information for Patients

Patients should be counseled that antibacterial drugs including ampicillin and sulbactam for injection should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ampicillin and sulbactam for injection is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by ampicillin and sulbactam for injection or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibacterial which usually ends when the antibacterial is discontinued. Sometimes after starting treatment with antibacterial, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibacterial. If this occurs, patients should contact their physician as soon as possible.

4.5 Interaction with other medicinal products and other forms of interaction

Drug Interactions:

Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with ampicillin and sulbactam for injection may result in increased and prolonged blood levels of ampicillin and sulbactam. The concurrent administration of allopurinol and ampicillin increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or the hyperuricemia present in these patients. There are no data with ampicillin and sulbactam for injection and allopurinol administered concurrently. Ampicillin and sulbactam for injection and aminoglycosides should not be reconstituted together due to the in vitro inactivation of aminoglycosides by the ampicillin component of ampicillin and sulbactam for injection.

Drug/Laboratory Test Interactions:

Administration of ampicillin and sulbactam for injection will result in high urine concentration of ampicillin. High urine concentrations of ampicillin may result in false positive reactions when testing for the presence of glucose in urine using Clinitest™, Benedict's Solution or Fehling's Solution. It is recommended that glucose tests based on enzymatic glucose oxidase reactions (such as Clinistix™ or Testape™)

be used. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with ampicillin and sulbactam for injection.

4.6 Fertility, pregnancy and lactation

Pregnancy

Reproduction studies have been performed in mice, rats, and rabbits at doses up to ten (10) times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ampicillin and sulbactam for injection. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. (see –PRECAUTIONS-Drug/Laboratory Test Interactions section)

Nursing Mothers

Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when ampicillin and sulbactam for injection is administered to a nursing woman.

Pediatric Use

The safety and effectiveness of ampicillin and sulbactam for injection have been established for pediatric patients

one year of age and older for skin and skin structure infections as approved in adults.

Use of ampicillin and sulbactam for injection in pediatric patients is supported by evidence from adequate and wellcontrolledstudies in adults with additional data from pediatric pharmacokinetic studies, acontrolled clinical trial conducted in pediatric patients and post-marketing adverse eventssurveillance. (see**PHARMACOLOGICAL PROPERTIES,THERAPEUTIC INDICATIONS,ADVERSE REACTIONS, POSOLOGY AND METHOD OF ADMINISTRATION**sections).

The safety and effectiveness of ampicillin and sulbactam for injection have not been established for pediatric patientsfor intra-abdominal infections.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Adult Patients:

Ampicillin and Sulbactam for injection is generally well tolerated. The following adverse reactions have been reported in clinical trials.

Local Adverse Reactions

Pain at IM injection site – 16%

Pain at IV injection site – 3%

Thrombophlebitis – 3%

Phlebitis – 1.2%

Systemic Adverse Reactions

The most frequently reported adverse reactions were diarrhea in 3% of the patients and rash in less than 2% of the patients.

Additional systemic reactions reported in less than 1% of the patients were: itching, nausea, vomiting, candidiasis, fatigue, malaise, headache, chest pain, flatulence, abdominal distension, glossitis, urine retention, dysuria, edema, facial swelling, erythema, chills, tightness in throat, substernal pain, epistaxis and mucosal bleeding.

Pediatric Patients: Available safety data for pediatric patients treated with Ampicillin and Sulbactam for injection demonstrate a similar adverse events profile to those observed in adult patients. Additionally, atypical lymphocytosis has been observed in one pediatric patient receiving Ampicillin and Sulbactam for injection.

Adverse Laboratory Changes

Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

Hepatic: Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH. Hematologic: Decreased hemoglobin, hematocrit, RBC, WBC, neutrophils, lymphocytes, platelets and increased lymphocytes, monocytes, basophils, eosinophils, and platelets. Blood Chemistry: Decreased serum albumin and total proteins.

Renal: Increased BUN and creatinine.

Urinalysis: Presence of RBC’s and hyaline casts in urine.

Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following have been identified during post-marketing use of ampicillin sodium/sulbactam sodium or other products containing ampicillin. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of their seriousness, frequency, or potential causal connection to ampicillin sodium/sulbactam sodium.

Blood and Lymphatic System Disorders: Hemolytic anemia, thrombocytopenic purpura, and agranulocytosis have been reported. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Some individuals have developed positive direct Coombs Tests during

treatment with Ampicillin and Sulbactam for injection, as with other beta-lactam antibacterials.

Gastrointestinal Disorders: Abdominal pain, cholestatic hepatitis, cholestasis, hyperbilirubinemia, jaundice, abnormal hepatic function, melena, gastritis, stomatitis, dyspepsia, black "hairy" tongue, and Clostridium difficile associated diarrhea (see **CONTRAINDICATIONS** and **WARNINGS** sections).

General Disorders and Administration Site Conditions: Injection site reaction.

Immune System Disorders: Serious and fatal hypersensitivity (anaphylactic) reactions (See **WARNINGS** section). Acute myocardial ischemia with or without

myocardial infarction may occur as part of an allergic reaction.

Nervous System Disorders: Convulsion and dizziness

Renal and Urinary Disorders: Tubulointerstitial nephritis

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, Acute generalized exanthematouspustulosis (AGEP), erythema multiforme, exfoliative dermatitis, and urticaria (see **CONTRAINDICATIONS** and **WARNINGS** sections).

4.9 Overdose

Neurological adverse reactions, including convulsions, may occur with the attainment of high CSF levels of beta-lactams. Ampicillin may be removed from circulation by hemodialysis. The molecular weight, degree of protein binding and pharmacokinetics profile of sulbactam suggest that this compound may also be removed by hemodialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Ampicillin is similar to benzyl penicillin in its bactericidal action against susceptible organisms during the stage of active multiplication. It acts through the inhibition of cell wall mucopeptide biosynthesis. Ampicillin has a broad spectrum of bactericidal activity against many gram-positive and gram-negative aerobic and anaerobic bacteria.(Ampicillin is, however, degraded by beta-lactamases and therefore the spectrum of activity does not normally include organisms which produce these enzymes).

A wide range of beta-lactamases found in microorganisms resistant to penicillins and cephalosporins have been shown in biochemical studies with cell free bacterial systems to be irreversibly inhibited by sulbactam. Although sulbactam alone possesses little useful antibacterial activity except against the Neisseriaceae, whole organism studies have shown that sulbactam restores ampicillin activity against

beta-lactamase producing strains. In particular, sulbactam has good inhibitory activity against the clinically important plasmid mediated beta-lactamases most frequently responsible for transferred drug resistance. Sulbactam has no effect on the activity of ampicillin against ampicillin susceptible strains.

The presence of sulbactam in the formulationof ampicillin and sulbactam for injection effectively extends the antibacterial spectrum of ampicillin to include many bacteria normally resistant to it andtootherbeta-lactamantibacterials.Thus,ampicillin and sulbactam for injectionpossessesthepropertiesofabroad-spectrumantibacterialandabeta-lactamaseinhibitor.

While in vitro studies have demonstrated the susceptibility of most strains of the following organisms, clinical efficacy for infections other than those included in the **THERAPEUTIC INDICATIONS**section has not been documented.

Gram-Positive Bacteria

Staphylococcus aureus (beta-lactamase and non-beta-lactamase producing), *Staphylococcus epidermidis* (beta-lactamase and non-beta-lactamase producing), *Staphylococcus saprophyticus* (beta-lactamase and non-beta-lactamase producing), Streptococcus faecalis[1] (Enterococcus), *Streptococcus pneumoniae*[1](formerly D. pneumoniae), *Streptococcus pyogenes*[1], *Streptococcus viridans*[1].

Gram-Negative Bacteria

Hemophilusinfluenzae (beta-lactamase and non-beta-lactamase producing), Moraxel a (Branhamella) *catarrhalis* (beta-lactamase and non-beta-lactamase producing), *Escherichia coli* (beta-lactamase and non-beta-lactamase producing), *Klebsiella species*(all known strains are beta-lactamase producing), *Proteus mirabilis* (beta-lactamase and non-beta-lactamase producing), *Proteus vulgaris, Providenciarettgeri, Providenciastuarti , Morganellamorganii,*and*Neisseriagonorrhoeae*(beta-lactamaseandnon-beta-lactamaseproducing).

Anaerobes

Clostridium species,[1]Peptococcus species,[1]Peptostreptococcus species, Bacteroides species, including B. fragilis.

These are not beta-lactamase producing strains and, therefore, are susceptible to ampicillin alone.

5.2 Pharmacokinetic properties

General

Immediately after completion of a 15-minute intravenous infusion of Ampicillin and Sulbactam for injection, peak serum concentrations of ampicillin and sulbactam are attained. Ampicillin serum levels are similar to those produced by the administration of equivalent amounts of ampicillin alone. Peak ampicillin serum levels ranging from

109 to 150 mcg/mL are attained after administration of 2000 mg of ampicillin plus 1000 mg sulbactam and 40 to 71 mcg/mL after administration of 1000 mg ampicillin plus 500 mg sulbactam. The corresponding mean peak serum levels for sulbactam range from 48 to 88 mcg/mL and 21 to 40 mcg/mL, respectively. After an intramuscular injection of 1000 mg ampicillin plus 500 mg sulbactam, peak ampicillin serum levelsranging from 8 to 37 mcg/mL and peak sulbactam serum levels ranging from 6 to 24 mcg/mL are attained.

The mean serum half-life of both drugs is approximately 1 hour in healthy volunteers.

Approximately 75 to 85% of both ampicillin and sulbactam are excreted unchanged in the urine during the first 8 hours after administration of Ampicillin and Sulbactam for injection to individuals with normal renal function. Somewhat higher and more prolonged serum levels of ampicillin and sulbactam can be achieved with the concurrent administration of probenecid.

In patients with impaired renal function the elimination kinetics of ampicillin and sulbactam are similarly affected, hence the ratio of one to the other will remain constant whatever the renal function. The dose of Ampicillin and Sulbactam for injection in such patients should be administered less frequently in accordance with the usual practice for ampicillin.

Ampicillin has been found to be approximately 28% reversibly bound to human serum protein and sulbactam approximately 38% reversibly bound.

The following average levels of ampicillin and sulbactam were measured in the tissues and fluids listed:

Table 2 Concentration of Ampicillin and Sulbactam for Injection in Various Body Tissues and Fluids

Fluid or Tissue	**Dose (grams) Ampicil in/Sulbactam**	**Concentration (mcg/mL or mcg/g) Ampicil in/Sulbactam**
Peritoneal Fluid	0.5/0.5 IV	7/14
Blister Fluid(Cantharides)	0.5/0.5 IV	8/20
Tissue Fluid	1/0.5 IV	8/4
Intestinal Mucosa	0.5/0.5 IV	11/18
Appendix	2/1 IV	3/40

Penetration of both ampicillin and sulbactam into cerebrospinal fluid in the presence of inflamed meninges has been demonstrated after IV administration of this product.

The pharmacokinetics of ampicillin and sulbactam in pediatric patients receiving this product are similar to those observed in adults. Immediately after a 15-minute infusion of 50 to 75 mg/kg body weight, peak serum and plasma concentrations of 82 to 446 mcg ampicillin/mL and 44 to 203 mcg sulbactam/mL were obtained. Mean half-life values were approximately 1 hour.

5.3 Preclinical safety data

No further information of relevance.

6. Pharmaceutical particulars

6.1 List of excipients

None.

6.2 Incompatibilities

Ampicillin should not be mixed with blood products or other proteinaceousfluids(e.g. protein hydrolysates) or with intravenous lipid emulsions

6.3 Shelf life

3 Years

Reconstituted product should be used immediately.

6.4 Special precautions for storage

Store below 30°C, away from light and moisture.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 Nature and contents of container

7ml molded glass vials sealed with halogenated butyl rubber stoppers withaluminiumcaps.

Pack sizes: 10 vials per box, 50 vials per box.

6.6 Special precautions for disposal and other handling

Ampicillin and Sulbactam vials are not suitable for multidose use. Any residual solution should be discarded.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

05905/07484/NMR/2019

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 3 May 2021

10. Date of revision of the text

29-Mar-2023