effectiveness in woman taking ampicillin, resulting in unplanned pregnancy. Although the association is weak, patients should be given the option to use an alternate or additional method of contraception while taking ampicillin.

Methotrexate: Concurrent use with penicillin has resulted in decreased clearance of methotrexate and in methotrexate toxicity. Patient should be closely monitored. Leucovorin dosages may need to be increased and administered for longer periods of time.

Probenecid: Probenecid decreases renal tubular secretion of ampicillin and Sulbactam when used concurrently; this effect results in increased and prolonged serum concentrations, prolonged elimination half-life and increased risk of toxicity.

Laboratory Tests Interactions: False-Positive glycosuria may be observed in urinalysis using Benedict's reagent, Fehling's reagents and Clinitest. Following administration of ampicillin to pregnant women, a transient decrease in plasma concentration of total conjugated estriol, estriol-glucoronide, conjugated estrone and estradiol has been noted. This effect may also occur with Ampicillin and Sulbactam for Injection.

Incompatibilities: Ampicillin and Sulbactam for Injection and aminoglycosides should be reconstituted and administered separately, due to the in vitro inactivation of aminoglycosides by any of the aminopenicillins.

Overdosage
Limited information is available on the acute toxicity of ampicillin sodium and sulbactam sodium in humans. Overdosage of Ampicillin and Sulbactam for injection would be expected to produce manifestations that are principally extensions of the adverse reactions reported with the drug. The fact that high CSF concentrations of ß-Lactam antibiotics may cause neurologic effects, including seizures, should be considered. Because ampicillin and sulbactam are both removed from the circulation by hemodialysis, these procedures may enhance elimination of the drug from the body if over dosage occurs in patients with impaired renal function.

Pharmacology
Pharmacodynamics: Biochemical studies with the cell -free bacterial systems have shown to be an irreversible inhibitor of most important ß-lactamases that occur in penicillin-resistant organisms. It possess significant antibacterial activity only against Neisseriaceae. Acinetobacter calcoaceticus, Bacteroids sp, Branhamella catarrhalis and Pseudomonas cepacia. The potential for sulbactam sodium's preventing the destruction of penicillins and cephalosporins by resistant organism was confirmed in whole organisms studies using resistant strains, in which sulbactam sodium exhibited marked synergistic effects with the penicillins and cephalosporins. Since Sulbactam also binds to some penicillin- proteins, some sensitive strains are rendered more susceptible to the combination than to ß-Lactam antibiotic alone.

The bacterial component of the combination is ampicillin which, like benzyl penicillin, acts against sensitive organisms during the stage of active multiplication by the inhibition of biosynthesis of cell wall mucopeptide.

Microbiology: Ampicillin and Sulbactam for injection is effective against a wide range of gram-positive and gram-negative bacteria including: Staphylococcus aureus and epidermidis (including penicillin- resistant and some methicillin-resistant strains); Streptococcus pneumoniae, Streptococcus faecalis and other Streptococcus sp; Haemophilus influenzae and parainfluenzae, (both ß-lactamase-positive and negative strains); Branhamella catarrhalis; anaerobes, including Bacteroides fragilis and related species; Escherichia coli, Klebsiella sp, Proteus sp (both indole-positive and indole-negative) Morganella morganii, Citrobacter and Enterobacter spp, Neisseria meningitides and Neisseria gonorrhoeae.

Pharmacokinetics: Ampicillin and Sulbactam for injection diffuses readily into most body tissues and fluids in the human. Penetration into the brain and spinal fluid is low except when meninges are inflamed. High concentrations of sulbactam and ampicillin are achieved in the blood following I.V or I.M administration and both components have a half-life of approximately 1hr. Most of Ampicillin and Sulbactam for injection is excreted unchanged in the urine.

Caution: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

Store at temperatures not exceeding 30°C

Availability: Ciltamin 1.5 g - USP Type I Glass vial w/orange coloured flip-off seal (Box of 1's)
Ciltamin 750 mg - USP Type I Glass vial w/green coloured flip-off seal (Box of 1's)

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Registration No.: Ciltamin 1.5 g (DR-XY39040) / Ciltamin 750 mg (DR-XY38898)
Date of First Authorization: February 10, 2011 / December 28, 2010
Revision Date: October 2018

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Km. 18, West Service Road,
SLEX, Parañaque City

Natrapharm

Ampicillin + Sulbactam

Ciltamin®

Formulation
Ciltamin 750: Each vial contains ampicillin (as sodium) 500mg and sulbactam (as sodium) 250mg.
Ciltamin 1.5: Each vial contains ampicillin (as sodium) 1000mg and sulbactam (as sodium) 500mg.

Indications
Used in the treatment of infections due to beta-lactamase producing H. influenzae including those of the respiratory tract, bones, joints and soft tissues, Polymicrobial infections with mixed aerobic and anaerobic such as diabetic foot, gynecologic infections, intra-abdominal infections and urinary tract infections due to susceptible organism.

Dosage
Ampicillin and sulbactam for Injection can be administered by either I.V or I.M routes. The following dilutions may be used.

Total Dosage (g)	Equivalent Dosage of Sulbactam - Ampicillin (g)	Package	Diluent Volume (mL)	Maximum Final Concentration (mg/mL)
0.75	0.25 - 0.5	15mL vial	1.6	125 - 250
1.5	0.5 - 1	15mL vial	3.2	125 - 250

For I.V. Administration, Ampicillin and Sulbactam for Injection should be reconstituted with sterile water for injection or any compatible solution. To ensure complete dissolution, allow foaming to dissipate in order to visually inspect. The dose can be given by bolus injection over a minimum of 3 min or can be used in greater dilutions as an I.V , infusion over 15 - 30 min.

Ampicillin and sulbactam for injection may also be administered by deep I.M injection; If pain is experienced, 0.5% sterile solution for injection of anhydrous lidocaine HCl may be used for reconstitution of the powder.

Adults: Usual Dosage Range: 1.5 - 12g/ day in divided doses every 6 or 8 hours up to a maximum daily dosage of sulbactam 4g. Less severe infections may be treated on an every -12- hour schedule.

Mild Infections: 1.5 (1g ampicillin as the sodium salt plus 0.5 g sulbactam as the sodium salt to 3g (2g ampicillin as the sodium salt plus 1 g sulbactam as the sodium salt) daily
Moderate Infections: Up to 6g daily (4g ampicillin as the sodium salt plus 2 g sulbactam as the sodium salt) daily
Severe Infections: Up to 12g daily (8g ampicillin as the sodium salt plus 4 g sulbactam as the sodium salt) daily

More or less frequent dosing may be indicated depending on the severity of the illness and the renal function of the patient. Treatment is usually continued until 48 hours after fever and other abnormal signs have resolved. Treatment is normally given for 5-14 days but the treatment period may be extended or additional ampicillin may be administered in severely ill cases.

In treating patients on restricted sodium intake, it should be noted that the 1500mg of ampicillin and Sulbactam for Injection contains approximately 115mg (5 mmol) of sodium.

Prophylaxis of Surgical Infections: 1.5 - 3g of Ampicillin and Sulbactam for Injection should be given at induction of anesthesia, which allows sufficient time to achieve effective serum and tissue concentrations during the procedure. The dose may be repeated every 6-8 hours; administration is usually stopped 24 hours after the majority of surgical procedures, unless a therapeutic course of Ampicillin and Sulbactam for Injection is indicated.

Treatment of Uncomplicated Gonorrhea: Ampicillin and Sulbactam for Injection can be given as a single dose of 1.5 g. Concomitant probenecid 1g orally should be administered in order to prolong plasma concentrations of Sulbactam and ampicillin.

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 300mg/kg/day dosage represents the total ampicillin content of Ciltamin and corresponds to 200mg/100mg sulbactam per kg per day. The safety and efficacy of Ciltamin 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.

Patients with severe Impairment of Renal Function (Creatinine Clearance ≤ 30mL/ min): The elimination kinetics of sulbactam and ampicillin are similarly affected and hence, the plasma ratio of one to the other

will remain constant. The dose of Ampicillin and sulbactam for injection in such patients should be administered less frequently in accordance with the usual practice for ampicillin.

Administration
Instructions for use: Sulbactam sodium is compatible with the most I.V solutions, but ampicillin sodium and hence Ampicillin and sulbactam for Injection is less stable in solutions containing dextrose or other carbohydrates and should not be mixed with the blood products or protein hydrolysates. Ampicillin and hence ampicillin and Sulbactam for injection is incompatible with aminoglycosides and should not be physically mixed in the same container. The concentrated solution for IM administration should be used within 1 hour of reconstitution. Time periods for use with different diluents for I.V infusion are as follows.

Diluent	Concentration Sulbactam + Ampicillin (mg/mL)	Use Periods in hours	
Water for Injection	IM: 375mg(potency)/mL IV: 45mg(potency)/mL	30°C	8 hours

Contraindications
Individuals with a history of an allergic reaction to any of the penicillins.

Warnings
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy, including Ampicillin and Sulbactam for Injection.
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 injury should be made concerning previous hypersensitivity reaction to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and the appropriate therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with adrenaline. Oxygen, I.V steroids and airway management, including intubation, should be administered as indicated.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ciltamin, 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 antibiotic 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 antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic 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 antibiotics should not be administered to patients with mononucleosis. In patients treated with ampicillin/sulbactam 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/sulbactam 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/sulbactam should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When ampicillin/sulbactam 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 UNASYN or other antibacterial drugs in the future.

Diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, 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 antibiotic. If this occurs, patients should contact their physician as soon as possible.

Drug Interactions: Probenecid decreases the renal tubular secretion of ampicillin and sulbactam. Concurrent use of probenecid with ampicillin/sulbactam 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/sulbactam and allopurinol administered concurrently. Ampicillin/sulbactam and aminoglycosides should not be reconstituted together due to the in vitro inactivation of aminoglycosides by the ampicillin component of Ciltamin.

Effects on the ability to drive or operate Machinery: Not known

Pregnancy Category B: 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 . 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).

Labor and Delivery: Studies in guinea pigs have shown that intravenous administration of ampicillin decreased the uterine tone, frequency of contractions, height of contractions, and duration of contractions. However, it is not known whether the use of ampicillin and sulbactam in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood that forceps delivery or other obstetrical intervention or resuscitation of the newborn will be necessary.

Nursing Mothers: Low concentrations of ampicillin and sulbactam are excreted in the milk; therefore, caution should be exercised when 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 well-controlled studies in adults with additional data from pediatric pharmacokinetic studies, a controlled clinical trial conducted in pediatric patients and post-marketing adverse events surveillance.

The safety and effectiveness of Ciltamin have not been established for pediatric patients for intra-abdominal infections.

Adverse Reactions
Ampicillin and Sulbactam for injection is generally well-tolerated. The majority of side effects observed were of mild or moderate severity and were normally tolerated with continued treatment.

As with other parental antibiotics, the principal side effect observed is injection site pain, especially associated with the I.M route of administration A small number of patients may develop phlebitis or an injections site reaction after I.V administration.

Body as a whole: Anaphylactoid reaction and anaphylactic shock.

Central and Peripheral Nervous : Rare reports of convulsions.

Gastrointestinal: The most frequently observed side effect was diarrhea/ loose stool. Nausea, Vomiting, epigastric distress and abdominal cramps have been observed. As with other ampicillin-class antibiotics, enterocolitis and pseudomembranous colitis rarely may occur.
Hematopoietic and Lymophatic: Hemolytic anemia, thrombocytopenia, eosinophilia and leukopenia have been reported during therapy with Ampicillin and Sulbactam. These reactions are reversible on discontinuation of therapy and are believed to be sensitivity reactions.

Liver/Biliary: Transient elevations of ALT (SGPT) and AST (SGOT) transaminases, bilirubinemia, abnormal hepatic function and jaundice.

Skin/Skin Structures: Common: Rash, Itching and other skin reactions were infrequently observed. Rare reports of Stevens-Johnsons syndrome, epidermal necrolysis and erythema multiforme were infrequently observed.

Urinary: Rare reports of Interstitial nephritis.

Others: Drowsiness/ Sedation, Fatigue / malaise and headache have been rarely observed.

Since infections mononucleosis is viral in origin, ampicillin should not be used in its treatment. A high percentage of patients with mononucleosis who received ampicillin have developed a skin rash.

Adverse reactions associated with the use of ampicillin alone may be observed with ampicillin and sulbactam for injection.

Drugs Interactions
Allopurinol: The concurrent administration of allopurinol and ampicillin substantially increases the incidence of rashes in patients receiving both drugs as compared with patients receiving ampicillin alone. There are no data concerning concurrent administration of ampicillin and sulbactam and allopurinol.

Aminoglycosides: Mixing ampicillin with aminoglycosides in vitro has resulted in substantial mutual inactivation; if these groups of antibacterials are to be administered concurrently, they should be administered at separate sites at least 1hr apart.

Anticoagulants: Parental penicillin can produce alterations in platelet aggregation and coagulation tests. These effects may be additive with anticoagulants.

Bacteriostic Drugs (chloramphenicol, Erythromycin, Sulfonamides and Tetracyclines): Basteriostatic drugs may interfere with the bactericidal effect of penicillins; it is best to avoid concurrent therapy.

Estrogen-Containing Oral Contraceptives: There have been case reports of reduced oral contraceptive