AmpiSulVenir 1.5 g
powder for solution for injection

AmpiSulVenir 3 g
Powder for solution for injection

1. NAME OF THE MEDICINAL PRODUCT
AmpiSulVenir 1.5 g
AmpiSulVenir 3 g

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each vial of AmpiSulVenir 1.5 g contains:

Ampicillin sodium	1063 mg	equivalent to	Ampicillin	1000 mg
Sulbactam sodium	547 mg	equivalent to	Sulbactam	500 mg

For a full list of excipients, see section 6.1

Each vial of AmpiSulVenir 3 g contains:

Ampicillin sodium	2132 mg	equivalent to	Ampicillin	2000 mg
Sulbactam sodium	1099 mg	equivalent to	Sulbactam	1000 mg

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM
White off white powder for solution for injection

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
AmpiSulVenir is antibiotic indicated for the treatment of bacterial infections caused by susceptible beta-lactamase producing strains of microorganisms, in the following conditions:
1. Skin and Skin Structure Infections
2. Intra- Abdominal Infections
3. Gynecological Infections

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

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

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

4.2 Posology and method of administration
Adult Patients and adolescent (over 40 kg)

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.

AmpiSulVenir may be administered by deep intramuscular injection.

The recommended adult dosage of AmpiSulVenir 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 of AmpiSulVenir, 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 of AmpiSulVenir 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 of AmpiSulVenir, and corresponds to 200 mg ampicillin/100 mg sulbactam per kg per day. The safety and efficacy of AmpiSulVenir 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 AmpiSulVenir.

- **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 of AmpiSulVenir in such patients should be administered less frequently in accordance with the usual practice for ampicillin and according to the following recommendations:

TABLE 1

AmpiSulVenir Dosage Guide For Patients With Renal Impairment

Creatinine Clearance (mL/min/1.73m^2)	**Ampicillin/Sulbactam Half-Life (Hours)**	**Recommended** AmpiSulVenir **Dosage**
≥30	1	1.5-3.0 g q 6h-q 8h
15-29	5	1.5-3.0 g q 12h
5-14	9	1.5-3.0 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.

$$\text{Males} \quad \frac{\text{weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$$

Females 0.85 × above value

Duration of administration

The treatment is usually continued until 48 hours after fever and abnormal signs have resolved. Treatment is normally administered for 5 to 14 days, but it should be prolonged or an additional dose of ampicillin should be administered in case of very severe infections. The total dosage of sulbactam should not exceed 4 g per

day.

Therapy over at least 10 days is indicated in the treatment of infections with beta-haemolytic streptococci in order to prevent late complications (e.g. rheumatic fever, glomerulonephritis).

Administration
The combination of ampicillin and sulbactam may be administered by either intramuscular or intravenous route.

Aminoglycosides are inactivated in vitro by ampicillin: therefore the mixing of aminoglycosides with ampicillin and sulbactam must be avoided in the solution for application. There should be a time limit of at least one hour between the separate applications. The site of injection of aminoglycosides should be different from that of Ampicillin and Sulbactam.

The following drugs should be applicated separately either, because there are incompatibilities, too: metronidazole, tetracycline- derivates, thiopental sodium, prednisolone, procaine 2%, suxamethoniumchloride and noradrenaline.

Intravenous use
*A*mpicillin and sulbactam can be reconstituted with water for injection or with compatible solutions. Ampicillin and sulbactam can be administered by bolus intravenous injection over at least 3 minutes or by intravenous infusion in 15 to 30 minutes (see section 6.6).

Intramuscular use
The sterile dry powder may be dissolved in water for injections or in lidocaine hydrochloride 5 mg/ml (0,5%) solution (see section 6.6). Ampicillin and sulbactam should be administered by deep intramuscular injection (for contraindications see section 4.3).

4.3 Contraindications
- Hypersensitivity (e.g., anaphylaxis or Stevens-Johnson syndrome) to ampicillin, sulbactam, or to other beta-lactam antibacterial drugs (e.g., penicillins and cephalosporins) or to any of the excipients
- Infections caused by herpetic viruses, in infective mononucleosis and in lymphatic leukaemia
- AmpiSulVenir must not be given in preterm and term newborn infants, infants and toddlers (below 2 years) by intramuscular application
- AmpiSulVenir with lidocaine for intramuscular injection is contraindicated during pregnancy and lactation (see 4.6)
- AmpiSulVenir is contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with AmpiSulVenir.

4.4 Special warnings and precautions for use

Hypersensitivity
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients treated with penicillins. 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 that have experienced severe reactions when treated with cephalosporins. Before starting a treatment with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other drugs/ allergens.
If an allergic reaction occurs, the treatment should be discontinued and the appropriate therapy instituted.
Serious anaphylactic reactions require an emergency treatment with adrenalin. Oxygen, intravenous steroids and airway management, including intubation, should also be administered when required.

Hepatotoxicity
Hepatic dysfunction, including hepatitis and cholestatic jaundice has been associated with the use of AmpiSulVenir. 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
AmpiSulVenir may cause severe skin reactions, such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), dermatitis exfoliative, erythema multiforme, and Acute generalized exanthematous pustulosis (AGEP). If patients develop a skin rash they should be monitored closely and AmpiSulVenir discontinued if lesions progress (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS** sections).

As for other systemic drugs, in case of prolonged therapy (more then one to two weeks) the monitoring of the function of the principal systems and apparatuses is recommended, including renal and hepatic systems and the haematopoietic system. The monitoring is very important in neonates, particularly in premature, and in the other paediatric patients.
In patients with impaired renal function the elimination kinetics of ampicillin and of sulbactam are similarly affected, hence the ratio of their plasmatic levels will remain constant.
The dose of ampicillin and sulbactam in such patients should be monitored, and less frequently administered, according to the usual practice for ampicillin.

In the treatment of patients who may assume a limited quantity of sodium it should be considered that the package of ampicillin 1 g and sulbactam 500 mg contains approximately 115 mg (5 mmol) of sodium.
In the treatment of patients who may assume a limited quantity of sodium it should be considered that the package of ampicillin 2 g and sulbactam 1 g contains approximately 230 mg (10 mmol) of sodium.

In case of severe and persistent diarrhoea, the possibility of pseudomembraneous colitis must be considered and if not refuted, therapy should be discontinued and appropriate measures should be taken. The use of antiperistaltics is contraindicated in such cases.
In neonates, the half-life of the two drugs substances is prolonged; it is approximately 7,9 hours for sulbactam and 9,4 hours for ampicillin. In these subjects the therapeutic dosage should be administered in two divided doses, according to the usual practice for ampicillin.
Ampicillin impairs colonic fermentation of carbohydrates and a diet high in unabsorbable carbohydrate increases the risk of antibiotic-associated diarrhoea. Consult a health practitioner to learn about sources of indigestible carbohydrates.

***Clostridium difficile*-Associated Diarrhea**
Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including AmpiSulVenir, 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 antibacterial should not be administered to patients with mononucleosis. In patients treated with AmpiSulVenir 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 AmpiSulVenir 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 AmpiSulVenir should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When AmpiSulVenir 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 AmpiSulVenir 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 Interactions with other medicinal products and other forms of interaction
Effects of other medicinal products
Acetylsalicylic acid, indomethacin and phenylbutazone decrease excretion of penicillins.

Allopurinol
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.

Oral hormonal contraceptives
Concurrent use of aminopenicillins and oral contraceptives has been connected with the possibility of decreased plasma level of oestrogens and progesterone and may reduce the efficacy of hormonal contraceptives.
Patients should be advised to use supplemental non-hormonal contraceptives measures.

Methotrexate
Concomitant administration with methotrexate may decreases the renal clearance of methotrexate and may lead to an increase of the toxicity of methotrexate. Serum methotrexate levels should be closely monitored.

Other antibiotics or chemotherapeutics
Aminopenicillins should not be used concomitantly with bacteriostatic antibiotics. There is a possibility that the antibacterial action of amoxicillin could be antagonised on co-administration with macrolides, tetracyclines, sulphonamides or chloramphenicol.

Aminoglycosides
AmpiSulVenir and aminoglycosides should not be reconstituted together due to the *in vitro* inactivation of aminoglycosides by the ampicillin component of AmpiSulVenir.
The mixing of aminoglycosides with ampicillin and sulbactam must be avoided in the solution for infusion.

Anticoagulants
With concurrent use of coumarin anticoagulants, such as warfarin, the effects of the anticoagulants may be increased. The changes in platelet aggregation and a prolongation of the prothrombin times has been observed.

Probenecid

Probenecid decreases the renal tubular secretion of ampicillin and sulbactam; therefore, its concurrent use of Probenecid with AmpiSulVenir may result in increased and prolonged blood levels of ampicillin and sulbactam.

Influence of laboratory tests

Administration of AmpiSulVenir 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 AmpiSulVenir.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential.

4.6 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. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response,

AmpiSulVenir should not be used during pregnancy unless clearly necessary. (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 AmpiSulVenir is administered to a nursing woman.

Supplying information for powder for solution for injection-intramuscular administration

Ampicillin and sulbactam with lidocaine is contraindicated during pregnancy. Controlled clinical trials and data of pregnant women are not available. Animal data reveal no undesirable effects on reproduction. In animal studies treatment with lidocaine showed some evidence on neurobehavioural changes but no embryotoxic and teratogenic effects were observed. Lidocaine passes into breast-milk in small amounts. Ampicillin and sulbactam with lidocaine is contraindicated during lactation.

Pediatric Use: The safety and effectiveness of ampicillin and sulbactam 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 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 ampicillin and sulbactam have not been established for pediatric patients for intra-abdominal infections.

4.7 Effects on ability to drive and use machines

Ampicillin and sulbactam may not have an influence on the ability to drive and use machines, but there are reports of undesirable effects (see section 4.8) and patients should know how they react to

ampicillin/sulbactam before they drive or operate machinery. These effects may be enhanced by alcohol.

4.8 Undesirable effects
Adult Patients: ampicillin and sulbactam 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 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.

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 , as with other beta-lactam antibacterials.
Very rare (< 1/10,000) **:**
Changes of the blood count such as reversible anaemia, leucopoenia, eosinophilia, Impairment of blood coagulation.

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).
meteorism can occur. If severe and persistent diarrhoea occurs, the possibility of antibiotic-related pseudomembranous colitis should be considered, which can be life-treating. Therefore in these cases Ampicillin/Sulbactam should be discontinued immediately and a suitable therapy (e.g. oral vancomycin 250

mg four times daily) instituted. Peristaltic-inhibiting drugs are contraindicated.

General Disorders and Administration Site Conditions: injection site reaction
Common (> 1/100, <1/10)
In some patients phlebitis or reactions in the area of the injection site may occur.
Rare (> 1/10,000 <1/1000):
Asthenia, sleepiness.

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.

Hypersensitivity reactions
Hypersensitivity reactions like urticaria, fever, maculopapular eruptions are possible.
If such symptoms occur, the drug should be discontinued and the doctor consulted.
An immediate reaction in the form of urticaria generally indicates a true penicillin allergy and requires discontinuation of the treatment.
Severe acute hypersensitivity reactions can appear such as: facial oedema, swelling of the tongue, swelling of the larynx narrowing of the airways, severe skin reactions such as erythema exudativum multiforme, tachycardia, dyspnoea, drug fever, eosinophilia, serum sickness, haemolytic anaemia, allergic vasculitis and nephritis, hypotension, anaphylactoid reaction, anaphylactic shock.
On occurrence of these signs, immediate medical assistance may be necessary.
Skin fungi and penicillin can share antigenic properties, so that hypersensitivity reactions as seen after a second contact may occur even on the first administration of a penicillin in a person currently or previously suffering from a fungal skin infection.

Nervous System Disorders: Convulsion and dizziness
Uncommon (> 1/1,000 <1/100) : Vertigo
Neurotoxic reactions (cramps) in events of meningitis or epilepsy, particularly after administration of high doses and impaired renal function respectively.

Renal and Urinary Disorders: Tubulointerstitial nephritis
Rare(> 1/10,000 <1/1000): interstitial nephritis; crystalluria by high intravenous dosage.

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Toxic epidermal necrolysis, Stevens-Johnson syndrome, angioedema, Acute generalized exanthematous pustulosis (AGEP), erythema multiforme, exfoliative dermatitis and urticaria (see **CONTRAINDICATIONS** and **WARNINGS** sections).
Uncommon (> 1/1,000 <1/100) : pruritus, and other skin reactions.
The typical, meales-like ampicillin rash (ampicillin-associated exanthema) that occurs 5 to 11 days after the start of the treatment, does not necessarily preclude subsequent treatment with penicillin derivates.

Hepato-biliary disorders
Very rare (< 1/10,000):
bilirubinaemia, abnormal liver function tests, jaundice.

Musculoskeletal, connective tissue and bone disorders
Very rare (< 1/10,000): Transient and minor increases of the creatinphosphokinase (CPK).

Adverse reactions usually associated with ampicillin alone may also occasionally occur with ampicillin/sulbactam. Further side effects which were described in rare cases for ampicillin such as arthralgia, stomatitis, black tongue discoloration, hereditary angioneurotic edema, exfoliative dermatitis and erythema multiform as well as the occurrence of an anaphylactic shock with a penicillin-hypersensitivity, can not be totally excluded with the use of ampicillin/sulbactam.

Reporting suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il/

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
Pharmacotherapeutic group:
Antibacterial for systemic use - ATC code: J01CR01

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 AmpiSulVenir formulation effectively extends the antibacterial spectrum of ampicillin to include many bacteria normally resistant to it and to other beta-lactam antibacterials. Thus, AmpiSulVenir possesses the properties of a broad-spectrum antibacterial and a beta-lactamase inhibitor

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 INDICATIONS and USAGE 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*† (Enterococcus), *Streptococcus pneumoniae*† (formerly *D. pneumoniae), Streptococcus pyogenes*†, *Streptococcus viridans*†.

Gram-Negative Bacteria: *Hemophilus influenzae* (beta-lactamase and non-beta-lactamase producing), *Moraxella (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, Providencia rettgeri, Providencia stuartii, Morganella morganii*, and *Neisseria gonorrhoeae* (beta-lactamase and non-beta-lactamase producing).

Anaerobes: *Clostridium* species,† *Peptococcus* species,† *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 AmpiSulVenir, 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 levels ranging 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 AmpiSulVenir 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 AmpiSulVenir in such patients should be administered less frequently in accordance with the usual practice for ampicillin (see DOSAGE and ADMINISTRATION section).

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 1
Concentration of AmpiSulVenir in Various Body Tissues and Fluids

Fluid or Tissue	Dose (grams) Ampicillin/Sulbactam	Concentration (mcg/mL or mcg/g) Ampicillin/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 AmpiSulVenir.

The pharmacokinetics of ampicillin and sulbactam in pediatric patients receiving AmpiSulVenir are similar to those observed in adults. Immediately after a 15-minute infusion of 50 to 75 mg AmpiSulVenir /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
Preclinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity and genotoxicity. Long-term studies to evaluate the cancerogenic potential have not been performed.
In embryotoxicity studies, the combination of ampicillin and sulbactam did not have teratogenic effects and in further studies no effects on fertility were observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Not applicable

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products excepting those mentioned in section 6.6

6.3 Shelf-life
The expiry date of the product is indicated on the packaging materials.
After reconstitution the solution has to be used immediately and any residue should be discarded.

6.4 Special precautions for storage
Below 30º C

6.5 Nature and contents of container
AmpiSulVenir 1.5G is presented in the following package:
- Cardboard box containing: Ampicillin/Sulbactam 1g + 500 mg powder in a 20 ml glass vial (10 powder vials)

AmpiSulVenir 3G is presented in the following package:
- Cardboard box containing: Ampicillin/Sulbactam 2g + 1g powder in a 20 ml glass vial (10 powder vials)

6.6 Special precaution for disposal and other handlings
For AmpiSulVenir 1.5G:
Intravenous use
Intravenous injection: the sterile dry powder in the vial should be reconstituted with about 3 ml of water for injection and should be administered by bolus intravenous injection over at least 3 minutes, after completed dissolution (see section 4.2).
Intravenous infusion: the sterile dry powder in the vial may be reconstituted with 50/100 ml of one of the compatible solutions (not water for injection) and should be administered by intravenous infusion in 15 to 30 minutes (see section 4.2).
AmpiSulVenir is compatible with the following solvent solutions:
- sodium chloride 9 mg/ml (0.9%) solution for infusion
- sodium lactate solution
- lactated Ringer's solution
- glucose 50 mg/ml (5%) solution for infusion
- saccarose 100 mg/ml (10%) solution for infusion

After reconstitution the solution should be used immediately and any residue should be discarded.
Intramuscular use
The sterile dry powder in the vial should be reconstituted with about 3 ml of water for injection or lidocaine hydrochloride 5 mg/ml (0,5%) solution (for contraindications see section 4.3). The solution should be administered by deep intramuscular injection (for contraindications see section 4.2)
After reconstitution the solution should be used immediately and any residue should be discarded.

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear and colorless.

For single use only. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.

For AmpiSulVenir 3G:

Intravenous use

Intravenous injection: the sterile dry powder in the vial should be reconstituted with about 6-7 ml of water for injection and should be administered by bolus intravenous injection over at least 3 minutes, after completed dissolution (see section 4.2).

Intravenous infusion: the sterile dry powder in the vial may be reconstituted with 100 ml of one of the compatible solutions (not water for injection) and should be administered by intravenous infusion in 15 to 30 minutes (see section 4.2).

AmpiSulVenir is compatible with the following solvent solutions:

- sodium chloride 9 mg/ml (0.9%) solution for infusion
- sodium lactate solution
- lactated Ringer's solution
- glucose 50 mg/ml (5%) solution for infusion
- saccarose 100 mg/ml (10%) solution for infusion

After reconstitution the solution should be used immediately and any residue should be discarded.

Intramuscular use

The sterile dry powder in the vial should be reconstituted with about 6-7 ml of water for injection or lidocaine hydrochloride 5 mg/ml (0,5%) solution (for contraindications see section 4.3). The solution should be administered by deep intramuscular injection (for contraindications see section 4.2)

After reconstitution the solution should be used immediately and any residue should be discarded.

The reconstituted solution should be inspected visually for particulate matter and discoloration prior to administration. The reconstituted solution is clear and colorless.

For single use only. Any unused solution and the vial should be adequately disposed of, in accordance with local requirements.

7. MANUFACTURER

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8. REGISTRATION HOLDER

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Herzliya Pituach 4666101

9. MARKETING AUTHORISATION NUMBERS

AmpiSulVenir 1.5G - 152-55-33564-00
AmpiSulVenir 3G - 152-56-33565-00

Revised on 12/21 according MoH guidelines