SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DEVASID 1.0 g Powder for IM/IV Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance:
Each vial contains:
Sulbactam 500.0 mg*
Ampicillin 1000.0 mg**
*Sulbactam sodium equivalent to sulbactam is used.
**Ampicillin sodium equivalent to ampicillin is used.

Excipients:
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Vial containing powder for injection and diluent liquid.
White or off-white colored powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DEVASID is indicated in infections caused by susceptible microorganisms. Typical indications are upper and lower respiratory tract infections including sinusitis, otitis media, epiglottis, bacterial pneumonias; urinary tract infections and pyelonephritis; intra-abdominal infections including peritonitis, cholecystitis, endometritis, and pelvic cellulitis; bacterial septicemia; skin, soft tissue, bone and joint infections and gonococcal infections.
DEVASID may be administered perioperatively to reduce the incidence of post-operative wound infections in patients undergoing abdominal or pelvic surgical interventions, in which peritoneal contamination may be present. DEVASID may be used prophylactically to reduce post-operative sepsis in termination of pregnancy or caesarean section.

4.2 Posology and method of administration

Posology/frequency and duration of administration:
DEVASID can be dissolved with the following amounts of lidocaine hydrochloride for intramuscular administration.

Ampicillin + Sulbactam Equivalent Doses (mg)	Total Dose (mg)	Package (vial)	Lidocaine Volume (ml)	Maximum Final Concentration (mg/ml)
250+125	375	10 ml	0.8	250+125
500+250	750	10 ml	1.6	250+125
1000+500	1500	20 ml	3.2	250+125
2000+1000	3000	20 ml	6.4	250+125

<u>Intravenous administration:</u>
DEVASID should be diluted with sterile water for injection or with a compatible solution (see section 6.6). Should be left for a while for visual inspection for possible foam to disappear and for complete dissolving. Dose can be given as bolus injection over 3 minutes or via intravenous infusions for 15-30 minutes in greater dilutions.

Intramuscular administration:
DEVASID should be diluted with sterile water for injection.
DEVASID can also be administered by deep intramuscular injection into a large muscle mass like the gluteus. Intramuscular injection should be administered, in 1 hour following reconstitution.
In case of pain in intramuscular administration, 0.5% sterile solution for injection of anhydrous lidocaine hydrochloride can be used in reconstitution.

Unless directed otherwise by a physician:
The usual daily dose range of DEVASID in adults with normal renal function is 1.5 g (1 vial of DEVASID 1 g corresponding to 1000 mg ampicillin + 500 mg sulbactam) to 12 g (8 vials of DEVASID 1 g corresponding to 8000 mg ampicillin + 4000 mg sulbactam). The maximum dose of sulbactam is 4 g per day. Daily doses of DEVASID are usually administered in divided doses every 6 to 8 hours. Not severe infections can be treated with doses administrated at 12-hour intervals.

Severity of Infection	Daily Dose of DEVASID (g)
Mild	1.5-3 g (1-2 g ampicillin + 0.5-1 g sulbactam)
Moderate	up to 6 g (4 g ampicillin + 2 g sulbactam)
Severe	up to 12 g (8 g ampicillin + 4 g sulbactam)

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

For the prophylaxis of surgical infections, 1.5-3 g of DEVASID (1-2 vials of DEVASID 1 g) should be administered 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. Prophylactic administration is usually discontinued 24 hours after the majority of surgical procedures unless a therapeutic course of DEVASID is indicated.

In the treatment of uncomplicated gonorrhea, a single dose of 1.5 g DEVASID (DEVASID 1 g vial) can be administered. In order to prolong plasma concentrations of sulbactam and ampicillin, concomitant probenecid 1.0 g orally should be administered.

Method of administration:
DEVASID can be administered intramuscularly or intravenously.

Additional information on special populations:
Renal/Hepatic impairment:
In patients with severe impairment of renal function (creatinine clearance <30 ml/min) the elimination kinetics of ampicillin and sulbactam are similarly affected and thus the plasma ratio of the one to the other will remain constant. Dose frequency in renal impairment should be extended as in general ampicillin administration.

Dosage administration of DEVASID for patients with impaired renal function:

Creatinine Clearance (ml/min 1.73 m^2)	Ampicillin/Sulbactam Half Life (hour)	Recommended DEVASID Dose
>30	1	1.5-3 g every 6-8 hours

15-29	5	1.5-3 g every 12 hours
5-14	9	1.5-3 g every 24 hours

Pediatric population
The dosage for most infections in children, infants and neonates is 150 mg/kg/day (corresponding to 100 mg/kg/day ampicillin plus 50 mg/kg/day sulbactam).
In children, infants and neonates dosing is usually every 6-8 hours in accordance with the usual practice for ampicillin. In neonates in the first week of life (particularly preterms) the recommended dose is 75 mg/kg/day (corresponding to 25 mg/kg/day sulbactam plus 50 mg/kg/day ampicillin) in dividing doses every 12 hours.

4.3 Contraindications
This combination is contraindicated in individuals with a history of an allergic reaction to any of the penicillins.

4.4 Special warnings and precautions for use
Severe occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy, including sulbactam sodium/ampicillin sodium. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity 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 initiating therapy with penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens. If an allergic reaction occurs, the drug should be discontinued and appropriate therapy instituted.

Serious anaphylactic reactions require immediate emergency treatment with adrenaline (epinephrine). Oxygen, intravenous steroids, and measures to keep airways open, including intubation should also be administered as indicated.

As with any antibiotic preparation, constant observation for signs of overgrowth of non-sensitive organisms, including fungi, is essential. When superinfection occur, the drug should be discontinued and/or appropriate therapy instituted.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including sulbactam sodium/ampicillin sodium, 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 *Clostridium difficile*.
Clostridium difficile produces toxins A and B which causes CDAD. As these infections can be refractory to antimicrobial therapy and may require colectomy, hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality. The possibility of CDAD must be considered in all patients who present with diarrhea following antibiotic use. Since CDAD has been reported to occur two months after the administration of antibacterial agents, careful medical history is necessary.
Antibiotic use except that against *C. difficile* should be discontinued if CDAD is suspected or confirmed. Management with fluids and electrolytes, protein supplementation, treatment with an antibacterial drug effective against *C. difficile*, and surgical assessment should be initiated.

As with any potent systemic agent, it is advisable to check periodically for organ system dysfunction during prolonged therapy; this includes renal, hepatic, hematopoietic systems. This is particularly important in neonates, especially when premature, and other infants.

Since infectious mononucleosis is viral in origin, DEVASID should be avoided for treatment. A high percentage of patients with mononucleosis who received ampicillin have developed a skin rash.

Each 1.5 g DEVASID (1000 mg ampicillin + 500 mg sulbactam) contains approximately 115 mg (5 mmol) sodium, which is should to be taken into consideration by patients on a controlled sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction
Sulbactam sodium is compatible with most of the intravenous solutions. However, ampicillin sodium (therefore sulbactam sodium/ampicillin sodium) is less stable in solutions containing dextrose or other carbohydrates and should not be mixed with substances obtained from blood serum or protein hydrolysates.

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.

Aminoglycosides: Mixing ampicillin with aminoglycosides *in vitro* has resulted in considerable mutual inactivation; if these groups of antibacterials are to be administered concurrently, they should be administered at different sites at a time interval of at least one hour (see section 6.2).

Anticoagulants: Parenteral penicillins may interfere with coagulation tests and platelet aggregation. These effects may be additive with anticoagulants.

Bacteriostatic drugs (chloramphenicol, erythromycin, sulphonamides, tetracyclines): Bacteriostatic drugs may interfere with the bactericidal activity of penicillins; It is recommended to avoid concomitant treatment.

Methotrexate*:* Concurrent administration with penicillins has led to reduced methotrexate clearance and in methotrexate toxicity. Patients should be closely monitored. The increased and prolonged administration of calcium folinate may be required.

Estrogen-containing oral contraceptives: There have been case reports of reduced effectiveness of oral contraceptives in women receiving ampicillin resulting in unplanned pregnancy. Although the association is weak, patients should be provided with the option to use an alternate or additional method of contraception while receiving ampicillin.

Probenecid: When administered concomitantly, probenecid decreases renal tubular secretion of ampicillin and sulbactam, which leads to higher and more persisting serum concentrations, prolonged elimination half life, and increased risk of toxicity.

Laboratory Test Interactions: False positive glucosuria may be observed in urinalysis using Benedict or Fehling reagents or Clinitest™. 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.

Additional information on special populations
Not available.

Pediatric population:
Not available.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category: B

Women of child-bearing potential/Birth control (Contraception)
Ampicillin interacts with orally administered oral contraceptives. Therefore, an alternative, effective and safe method of contraception should be used during treatment (see section 4.5).

Pregnancy
No clinical data concerning DEVASID exposure in pregnant women are available.
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy/ embryonal/fetal development/parturition or post-natal development (see section 5.3).
This drug should be used in pregnant women only if absolutely necessary.

Breast-feeding
Safety of sulbactam and ampicillin for use in lactation has not been established.
Since sulbactam and ampicillin are excreted into human breast-milk, caution should be exercised when it is administered during breast-feeding.

Fertility
In animal reproduction studies, no harmful effects on fertility and fetus were determined.

4.7 Effects on ability to drive and use machines
Not known.

4.8 Undesirable effects
As with other parenteral antibiotics, the principal undesirable effect observed is injection site pain (16%) in particular associated with intramuscular administration. Phlebitis (3%) and pain at injection site (3%) may be seen in very few patients after intravenous administration.

Blood and lymphatic system disorders
Anemia, hemolytic anemia, thrombocytopenia, eosinophilia and leucopenia have been reported during sulbactam sodium/ampicillin sodium treatment. These reactions are reversible on discontinuation of the drug and are believed to be sensitivity reactions.

Immune system disorders
Anaphylactoid reaction and anaphylactic shock may occur.

Nervous system disorders
Rare reports of convulsion, vertigo-dizziness and headache.

Gastrointestinal disorders
Nausea, vomiting and diarrhea are the most commonly observed undesirable effects. Enterocolitis and pseudomembranous colitis may also occur.

Hepatobiliary disorders

Bilirubinemia, abnormal liver function and jaundice have been reported.

Skin and subcutaneous tissue disorders
Rash, pruritus and other skin reactions are the most frequently reported undesirable effects. In rare cases Stevens-Johnson syndrome, epidermal necrolysis and erythema multiforme were observed.

Renal and urinary disorders
Rare reports of interstitial nephritis.

Investigations
Transient increase in ALT (SGPT) and AST (SGOT)

Undesirable effects observed with ampicillin administration alone may be observed with sulbactam sodium/ampicillin sodium IM/IV administration.

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions in accordance with local requirements.

4.9 Overdose
Limited information is available on the acute toxicity of sulbactam sodium/ampicillin sodium. Overdose of the drug would be expected to induce manifestations that are primarily extensions of the undesirable effects reported with the drug. The fact that high CSF concentrations of ß-lactam antibiotics may induce neurologic effects, including seizures, should be taken into consideration. Since sulbactam and ampicillin are both removed from the circulation by hemodialysis, these procedures may facilitate elimination of the drug from the body if overdose occurs in patients with renal impairment.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterials for systemic use
ATC code: J01CR04

Sulbactam has been shown in biochemical studies with cell-free bacterial systems to be an irreversible inhibitor of most important ß-lactamases that occur in penicillin-resistant organisms. While sulbactams antibacterial activity is mainly limited to *Neisseriaceae*, the potential for sulbactam sodium in preventing the destruction of penicillins and cephalosporins was confirmed in studies using resistant strains, in which sulbactam sodium exhibited marked synergistic effects with penicillins and cephalosporins. Since sulbactam also binds to penicillin-binding proteins, some susceptible strains are rendered more susceptible to the combination than to the beta-lactam antibiotic alone.

The bactericidal 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.

DEVASID 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* spp.; *Hemophilus influenza* and *parainfluenzae* (both beta-lactamase positive and negative strains); *Branhamella catarrhalis*; anaerobes, including *Bacteroides fragilis* and related species; *Escherichia coli*, *Klebsiella* species, *Proteus* species (both indole-positive and indol-negative); *Morganella morganii*; *Citrobacter* species; *Enterobacter* species; *Neisseria meningitidis* and *Neisseria gonorrhoeae*.

It should be considered that *Pseudomonas*, *Citrobacter* and *Enterobacter* species, which are known to be resistant to ampicillin, are not susceptible to sulbactam/ampicillin.

5.2 Pharmacokinetic properties
General properties
Sulbactam sodium is a derivative of the basic penicillin nucleus. Chemically, it is sodium penicillinate sulfone. It is a whitish crystalline powder that is very soluble in water. It has a molecular weight of 255.22. Ampicillin sodium is derived from the penicillin nucleus, 6-aminopenicillanic acid. Chemically, it is D(-)-α-aminobenzyl penicillin sodium salt and has a molecular weight of 371.39.

Distribution:
Sulbactam/ampicillin diffuses readily into most body tissues and fluids in the human.
Penetration into brain and spinal fluid is low except when meninges are inflamed. High concentrations of sulbactam and ampicillin are reached in the blood following intravenous and intramuscular administration and both components have a half-life of approximately 1 hour.

Elimination:
Most of the sulbactam/ampicillin is excreted unchanged in the urine.

5.3 Preclinical safety data
LD_{50} (with oral administration) has been found to be 8 g/kg in mice and higher than 4 mg/kg in rats for both male and female subjects.

In long-term studies performed in rats and dogs oral DEVASID has caused no profound histopathological lesions associated with major organs and systems. Similarly, studies carried out to evaluate potential fetal toxicity, teratogenicity, and fertility inhibition of DEVASID have revealed no such effects. Sulbactam/ampicillin combination has showed no mutagenic effects.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Vial:
None.
Diluent:
Water for injection.

6.2 Incompatibilities
Due to *in vitro* inactivation of aminoglycosides by any of the aminopenicillins, sulbactam sodium/ampicillin sodium and aminoglycosides should be reconstituted and administered separately.

6.3 Shelf life
36 months.

6.4 Special precautions for storage
Store at room temperature below 25°C.
The solution for intramuscular administration should be used within 1 hour after reconstitution.
The shelf lives for various solutions used in intravenous infusion are given in the package leaflet (see section 6.6).

6.5 Nature and contents of container
15 ml-colorless glass vial closed with a rubber stopper and sealed with an aluminum safety cap and 4 ml-ampoule containing 3.5 ml water for injection.
Each carton box contains 1 vial and 1 diluent ampoule as placed in a transparent PVC separator.

6.6 Special precautions for disposal and other handling
Sulbactam sodium is compatible with most of the intravenous solutions; but ampicillin sodium and therefore DEVASID IM/IV is less stable in solutions containing dextrose or other carbohydrates and should not be mixed with blood products or protein hydrolysates.

The solution for intramuscular administration should be used within 1 hour after reconstitution.

Use periods for various diluents for intravenous infusion are indicated below.

Diluent	Ampicillin/Sulbactam Concentration	Use Periods
Sterile Water for injection	up to 45 (mg/ml)	8 hours at 25°C
	45 (mg/ml)	48 hours at 4°C
	up to 30 (mg/ml)	72 hours at 4°C
Isotonic sodium chloride	up to 45 (mg/ml)	8 hours at 25°C
	45 (mg/ml)	48 hours at 4°C
	up to 30 (mg/ml)	72 hours at 4°C
M/6 Sodium lactate Solution	up to 45 (mg/ml)	8 hours at 25°C
	up to 45 (mg/ml)	8 hours at 4°C
5% Dextrose/water	15-30 (mg/ml)	2 hours at 25°C
	up to 3 (mg/ml)	4 hours at 25°C
	up to 30 (mg/ml)	72hours at 4°C
5% Dextrose / 0.45 NaCl	up to 3 (mg/ml)	4 hours at 25°C
	up to 15 (mg/ml)	4 hours at 4°C
10% inverted sugar/water	up to 3 (mg/ml)	4 hours at 25°C
	up to 30 (mg/ml)	3 hours at 4°C
Lactated ringer's solution	up to 45 (mg/ml)	8 hours at 25°C
	up to 45 (mg/ml)	24 hours at 4°C

Any unused material should be disposed according to local disposal regulations.

7. MARKETING AUTHORIZATION HOLDER
DEVA HOLDING A.Ş.
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8. MARKETING AUTHORIZATION NUMBER
202/60

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION
Date of first authorization : 06.06.2003
Date of last renewal :

10. DATE OF REVISION OF THE TEXT
04.01.2013