Public Assessment Report

Decentralised Procedure

Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion

Ampicillin sodium and Sulbactam sodium

UK/H/4322/001-2/DC

UK licence no: PL 28176/0047-8

Strides Arcolab International Limited
Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion

PL 28176/0047-8

LAY SUMMARY

On 24th May 2012, Austria, Bulgaria, Czech Republic, Germany, Italy, Poland, Slovak Republic and the United Kingdom agreed to grant marketing authorisations to Strides Arcolab International Limited for medicinal products Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion. The marketing authorisations were granted via the Decentralised Procedures (DCP), with the UK as Reference Member State (RMS). After the national phase, licences were granted in the UK on 2nd July 2012.

Ampicillin/Sulbactam is an antibiotic and works by killing bacteria that cause infections. It contains two different medicines called ampicillin and sulbactam. Ampicillin belongs to a group of medicines called ‘penicillins’ and sulbactam belongs to a group of medicines called ‘beta-lactam inhibitors’.

Ampicillin/Sulbactam is used in adults and children to treat the following
- Pneumonia
- Kidney infections
- Intra-abdominal infections
- Genital organ infection in women
- Skin and soft tissues infections

Ampicillin / Sulbactam is used to prevent infections associated with abdominal infections.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion outweigh the risks, hence Marketing Authorisations have been granted.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Module 1: Information about initial procedure</th>
<th>Page 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Module 2: Summary of Product Characteristics</td>
<td>Page 5</td>
</tr>
<tr>
<td>Module 3: Product Information Leaflets</td>
<td>Page 28</td>
</tr>
<tr>
<td>Module 4: Labelling</td>
<td>Page 32</td>
</tr>
<tr>
<td>Module 5: Scientific Discussion</td>
<td>Page 35</td>
</tr>
<tr>
<td>1 Introduction</td>
<td></td>
</tr>
<tr>
<td>2 Quality aspects</td>
<td></td>
</tr>
<tr>
<td>3 Non-clinical aspects</td>
<td></td>
</tr>
<tr>
<td>4 Clinical aspects</td>
<td></td>
</tr>
<tr>
<td>5 Overall conclusions</td>
<td></td>
</tr>
<tr>
<td>Module 6 Steps taken after initial procedure</td>
<td></td>
</tr>
</tbody>
</table>
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
</tr>
</tbody>
</table>
| **Active Substance** | Ampicillin sodium  
Sulbactam sodium |
| **Form** | Powder for Solution for Injection or Infusion |
| **Strength** | 1 g or 2 g Ampicillin Sodium  
0.5g or 1 g Sulbactam sodium |
| **MA Holder** | Strides Arcolab International Limited,  
Unit 4, Metro Centre,  
Tolpits Lane,  
Watford,  
Hertfordshire,  
WD 189 SS,  
UK |
| **RMS** | UK |
| **CMSs** | Austria, Bulgaria, Czech Republic, Germany, Italy, Poland and Slovak Republic |
| **Procedure Number** | UK/H/4322/001-2/DC |
| **Timetable** | Day 210: 24th May 2012 |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Ampicillin / Sulbactam 1 g/0.5 g Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substances: sulbactam sodium, ampicillin sodium

Ampicillin / Sulbactam 1 g/0.5 g:
Each vial with 1610 mg powder contains 547 mg sulbactam sodium, equivalent to 0.5 g sulbactam, and
1063 mg ampicillin sodium, equivalent to 1 g ampicillin.
Excipient: 5 mmol (115 mg) of sodium/vial of powder for solution for injection or infusion.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion
White to off-white powder

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Ampicillin / Sulbactam is indicated in the treatment of the following
- community acquired pneumonia
- upper urinary tract infection
- intra-abdominal infections
- gynaecological infections (see section 5.1)
- skin and soft tissues infections
- Prophylaxis against infections associated with abdominal surgery.

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

4.2 Posology and method of administration
Posology
The recommended dose for adults is 3 to 12 g Ampicillin / Sulbactam depending on
the severity of the infection divided into equal single doses every 6 to 8 hours.

Paediatric patients:
For children over 2 years the recommended dose is 150 mg/kg/day (ampicillin 100 mg/kg/day
+ sulbactam 50 mg/kg/day). The therapeutic dosage should be given in three or four divided doses.

The intramuscular application should not be given in newborn infants, infants and toddlers (below 2
years). Ampicillin / Sulbactam should be given exclusively by intravenous use according to the
following indications:
- For newborn infants above the second living week, infants and toddlers till 2 years the
  recommended dose is 150 mg/kg/day (ampicillin 100 mg/kg/day + sulbactam 50 mg/kg/day).
  The therapeutic dosage should be given in three or four divided doses.
- For newborn infants in the first living-week the recommended dose is 75 mg/kg /day
  (equivalent to ampicillin 50 mg/kg/day plus sulbactam 25 mg/kg/day). The therapeutic dosage
  should be given in two divided doses.

Use in the Elderly: Ampicillin / Sulbactam injection may be administered in the elderly in the usual
dosages with no special precautions.

Prophylaxis of surgical infections: 1.5 - 3g of Ampicillin / Sulbactam injection should be given at
induction of anaesthesia, which allows time to achieve effective serum and tissue concentrations during
the procedure. In case of long-term surgery another dose in 3-4 hours may be administered.
Administration of Ampicillin / Sulbactam is usually stopped 24 hours after the majority of surgical
procedures unless a therapeutic course of is indicated.
Use in patients with renal impairment:
In patients with severe renal impairment (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 whatever the renal function is. The dose of Ampicillin / Sulbactam in such patients should be administered less frequently in accordance with the usual practice for ampicillin.

### Recommended dosages for patients with impaired renal function:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml / min)</th>
<th>Dose interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>6 to 8 hours</td>
</tr>
<tr>
<td>15 to 30</td>
<td>12 hours</td>
</tr>
<tr>
<td>5 to 14</td>
<td>24 hours</td>
</tr>
<tr>
<td>&lt;5</td>
<td>48 hours</td>
</tr>
</tbody>
</table>

Sulbactam and ampicillin are both eliminated from the blood stream to an equal extent by hemodialysis treatment. Ampicillin / Sulbactam should therefore be administered immediately after dialysis and then at 48 hour intervals until the following dialysis treatment.

Use in patients with hepatic impairment: Usual recommended doses.

**Method of administration**
Please refer to section 6.6.

**Duration of use**
The duration of treatment depends on the course of the illness. The duration of treatment is generally 5 to 14 days depending on the severity of the infection. In severe cases, treatment may be continued for a prolonged period. The treatment should be continued for another 48 hours after the fever and other symptoms of the disease have subsided.

### 4.3 Contraindications

Hypersensitivity to the active substances, (ampicillin and sulbactam); to any other penicillin or to any of the excipients listed in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

### 4.4 Special warnings and precautions for use

Before initiating therapy with ampicillin/sulbactam, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

Severe and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin or cephalosporins hypersensitivity and in atopic individuals. If an allergic reaction occurs, ampicillin/sulbactam therapy must be discontinued and appropriate alternative 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.

Before starting a treatment with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

Ampicillin/sulbactam should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy (more than 14 days). The monitoring is very important in neonates, and in the other paediatric patients.

As with every antibiotic therapy, the physician should be alert to signs of overgrowth of non-sensitive organisms (including fungi). As soon as an infection with these organisms occurs, the product should be discontinued and / or suitable treatment instituted.
PAR Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

During treatment with Ampicillin / Sulbactam, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

Administration of ampicillin may reduce the efficacy of oral contraceptives. Supplemental non-hormonal contraceptive measures may be required.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including ampicillin / sulbactam and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic- associated colitis occur, Ampicillin / Sulbactam should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation.

Ampicillin / Sulbactam 1 g/0.5 g: This medicinal product contains 5 mmol (115 mg) of sodium/vial of powder for solution for injection or infusion. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products:
Acetylsalicylic acid, indometacin and phenylbutazone decrease excretion of penicillins.

Other antibiotics or chemotherapeutic agents
Ampicillin / sulbactam should not be combined with bacteriostatic chemotherapeutics or antibiotics such as tetracyclines, erythromycin, sulphonamides or chloramphenicol due to the possibility of reduced effectiveness.

Aminoglycosides are inactivated in vitro by ampicillin: therefore the mixing of aminoglycosides with ampicillin and sulbactam must be avoided in the solution for infusion. If concomitant treatment is necessary the two substances should be administered at different sites at a time interval of at least one hour. (see section 6.2)

Allopurinol
In gout patients being treated with allopurinol, simultaneous treatment with ampicillin / sulbactam increases the likelihood of cutaneous reactions.

Anticoagulants
The changes in platelet aggregation and prothrombin time observed with parenterally administered penicillins may be increased on simultaneous administration of anticoagulants.

Methotrexate
The concurrent administration of methotrexate and penicillins resulted in reduced methotrexate clearance and consequentially in methotrexate toxicity. These patients should be closely monitored and the increased and prolonged administration of Leucovorin should be considered.

Probenecid
The concomitant administration of probenecid leads to higher and more persisting ampicillin and sulbactam concentrations in serum and ampicillin concentrations in the bile due to inhibition of renal elimination (tubular secretion).

Hormonal contraceptives
During treatment with aminopenicillins, the reliability of the contraceptive effect of hormonal contraceptives ("the pill") may be compromised in rare cases. It is therefore recommended to additionally use non-hormonal methods of contraception.

Influence of laboratory tests
A high concentration of ampicillin in urines may result in false positive values of glucosuria. The use of glucose tests based on enzymatic glucose oxydase reactions is recommended.
4.6 Fertility, Pregnancy and lactation

Fertility

In animal studies, ampicillin and sulbactam had no effect on fertility (see section 5.3).

Pregnancy

Data on a limited number of exposed pregnancies indicate no adverse effects of Ampicillin and Sulbactam on pregnancy or on the health of the foetus/newborn child. However, data on first trimester exposure are lacking. In animal studies with ampicillin and sulbactam no teratogenicity was observed (see section 5.3). Ampicillin /Sulbactam should not be used during pregnancy unless clearly necessary.

Lactation

Ampicillin and sulbactam are excreted into human breast-milk. Although excretion of both drugs is low, diarrhoea and fungus infection of the mucous membranes and allergic sensitization could occur in the breast-fed infant. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Ampicillin /Sulbactam should be made taking into account the benefit of breast-feeding to the child and the benefit of Ampicillin / Sulbactam therapy to the woman.

4.7 Effects on ability to drive and use machines

No studies on the ability to drive and use machines under influence of ampicillin and sulbactam have been carried out. However, patients should be made aware that due to undesirable effects (see section 4.8) the reactivity may be decreased.

4.8 Undesirable effects

The following undesirable effects have been observed and reported during treatment with ampicillin / sulbactam with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data)

The most common undesirable effects are pain at the injection site, phlebitis, nausea, vomiting, meteorism and diarrhea. For severe and persistent diarrhea, the possibility of potentially fatal antibiotic-associated pseudomembranous colitis should be considered. In these cases, Ampicillin / Sulbactam should therefore be discontinued immediately and a suitable therapy (e.g. oral vancomycin 4 x 250 mg daily) instituted. Drugs that inhibit peristalsis are contraindicated.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Not known</td>
<td>Overgrowth of non-sensitive organisms</td>
</tr>
<tr>
<td>Blood and lymphatic system</td>
<td>Very rare</td>
<td>Hematocytological changes such as reversible and haemolytical anemia, thrombocytopenia, eosinophilia and leucopenia. Impairment of blood coagulation.</td>
</tr>
<tr>
<td>disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>--------</td>
<td>-----------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Severe acute hypersensitivity reactions</strong> can appear such as: facial oedema, swelling of the tongue, swelling of the larynx narrowing of the airways, severe skin reactions such as erythema exsudativum multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis (Leyell syndrome), 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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td>Uncommon</td>
<td>Vertigo and headache. Neurotoxic reactions (cramps) in events of meningitis or epilepsy, particularly after administration of high doses and impaired renal function respectively.</td>
</tr>
<tr>
<td>Disorder Type</td>
<td>Frequency</td>
<td>Description</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea, vomiting, meteorism and diarrhoea can occur. If severe and persistent diarrhoea occurs, the possibility of antibiotic-related pseudomembranous colitis should be considered, which can be life-threatening. Therefore in these cases Ampicillin/Sulbactam should be discontinued immediately and a suitable therapy (e.g. oral vancomycin 250 mg four times daily) instituted. Peristaltis-inhibiting drugs are contraindicated.</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare</td>
<td>Transient and reversible increase in transaminases (SGOT[ALT], SGPT [AST], bilirubinaemia, abnormal liver function tests, jaundice</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Uncommon</td>
<td>Rash, pruritus and other cutaneous 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.</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Very rare</td>
<td>Transient and minor increase of creatinephosphokinase (CPK)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>Rare</td>
<td>Interstitial Nephritis, crystalluria by high intravenous dosage.</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Very common</td>
<td>Intramuscular injection may be followed by pain at the injection site.</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Intravenous administration may be followed by phlebitis or pain at the injection site. Diarrhoea</td>
</tr>
</tbody>
</table>
Rare

As with other parenteral antibiotics, pain at the injection site particularly in connection with an intravenous administration were reported as primary side effects. In some patients phlebitis or reactions in the area of the injection site may occur. Asthenia, sleepiness. Adverse reactions usually associated with ampicillin alone may also occasionally occur with ampicillin/sulbactam: Arthralgia, stomatitis, black tongue discoloration, agranulocytosis, hereditary angioneurotic edema, exfoliative dermatitis and erythema multiform as well as the occurrence of an anaphylactic shock with a penicillin-hypersensitivity.

4.9 Overdose

Only limited experience is available for the acute toxicity of ampicillin / sulbactam. Overdose may induce symptoms corresponding to the undesirable effect profile (see Section 4.8) of Ampicillin / Sulbactam. In such cases, these described undesirable effects may possibly be observed more frequently and in a more severe form. In very high doses, beta-lactam antibiotics can induce cerebral (epileptic) seizures. Since ampicillin and sulbactam can be removed by hemodialysis, in the event of overdose, higher elimination can be achieved by hemodialysis in patients with renal impairment.

Treatment
Sedation with diazepam for seizures resulting from overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors, ATC code: J01CR01

Mechanism of action
Ampicillin is a semi-synthetic, non beta-lactamase-resistant aminopenicillin. Sulbactam is a beta-lactamase inhibitor with a structure similar to that of ampicillin and other penicillins.

The mechanism of action of ampicillin is based on inhibition of bacterial wall synthesis (in the growth phase) via blockade of the penicillin-binding proteins (PBPs) such as the transpeptidases. This results in a bactericidal action.

In combination with sulbactam, the inactivation of ampicillin by certain beta-lactamasases is inhibited. Sulbactam protects ampicillin from degradation by most beta-lactamasases of staphylococci and several plasmid-encoded beta-lactamasases (e.g. TEM, OXA) and certain chromosomally encoded beta-lactamasases of gram-negative bacteria. These beta-lactamasases are present in, for example, Escherichia coli, Klebsiella spp., Proteus mirabilis and Haemophilus influenzae. The antibacterial spectrum of action of ampicillin is broadened to include bacteria whose beta-lactamasases are inhibited by sulbactam.

PK/PD Relationship
The efficacy depends mainly on the time period for which the active substance level of ampicillin remains above the minimal inhibitory concentration (MIC) of the microorganism.

Mechanisms of resistance
Resistance to ampicillin/sulbactam can be due to the following mechanisms:

- Inactivation by beta-lactamasases: ampicillin/sulbactam does not have sufficient activity against beta-lactamase-producing bacteria whose beta-lactamasases are not inhibited by sulbactam.
- Reduced affinity of PBPs for ampicillin: the acquired resistance of pneumococci and other streptococci against ampicillin/sulbactam is due to the modification of existing PBPs as the result of a mutation. Methicillin (oxacillin)-resistant staphylococci are resistant due to the formation of an additional PBP with reduced affinity for ampicillin and all other beta-lactam
antibiotics.

- Insufficient penetration of ampicillin through the outer cell wall of gram-negative bacteria can result in inadequate inhibition of the PBPs.
- Ampicillin can be actively extruded from the cell by efflux pumps.

Partial or complete cross-resistance of ampicillin/sulbactam exists with penicillins, cephalosporins and other beta-lactam/beta-lactamase inhibitor combinations.

**Breakpoints**

MIC breakpoints for Ampicillin / Sulbactam are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterobacteriaceae</td>
<td>-</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td>Enterococcus spp</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>≤ 1 mg/l</td>
<td>&gt; 1 mg/l</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>≤ 1 mg/l</td>
<td>&gt; 1 mg/l</td>
</tr>
<tr>
<td>Staphylococcus spp</td>
<td>≤ 0.12</td>
<td>&gt; 0.12</td>
</tr>
<tr>
<td><em>Streptococcus A, B, C G</em></td>
<td>≤ 0.25</td>
<td>&gt; 0.25</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>≤ 0.06</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Gram-negative anaerobes</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td>Gram-positive anaerobes</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
</tbody>
</table>

Non species-specific limit values* ≤ 2 mg/l > 8 mg/l

1 For susceptibility testing purposes, the concentration of sulbactam is fixed at 4 mg/L
2 Susceptibility is inferred from amoxicillin-clavunate
3 Breakpoints values are based on benzylpenicillin breakpoints

**Susceptibility**

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable.

Organism susceptibility to ampicillin/sulbactam observed in the European clinical studies conducted in adults or children with various infections have been summarized in the following table.

It must be noted that this information gives only an approximate guidance on the probability that a micro-organism will be susceptible to Ampicillin / Sulbactam.
## Commonly susceptible species

<table>
<thead>
<tr>
<th>Aerobic gram-positive microorganisms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> (methicillin-sensitive)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus agalactiae</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em> (incl. penicillin-intermediate strains)</td>
<td></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
<td></td>
</tr>
<tr>
<td><em>Streptococci of the &quot;Viridans group&quot;</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aerobic gram-negative microorganisms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td></td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td></td>
</tr>
<tr>
<td><em>Neisseria gonorrhoeae</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Anaerobic microorganisms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacteroides fragilis</em></td>
<td></td>
</tr>
<tr>
<td><em>Fusobacterium nucleatum</em></td>
<td></td>
</tr>
<tr>
<td><em>Prevotella spp.</em></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other microorganisms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Gardnerella vaginalis</em></td>
<td></td>
</tr>
</tbody>
</table>

## Species for which acquired resistance may be a problem

<table>
<thead>
<tr>
<th>Aerobic gram-positive microorganisms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterococcus faecium</em>+</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em>+</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em>+</td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus hominis</em>+</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Aerobic gram-negative microorganisms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella oxytoca</em></td>
<td></td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td></td>
</tr>
<tr>
<td><em>Proteus vulgaris</em></td>
<td></td>
</tr>
</tbody>
</table>

**Inherently resistant organisms Aerobic**
gram-positive microorganisms
Staphylococcus aureus (methicillin-resistant)

Aerobic gram-negative microorganisms
Acinetobacter baumannii
Citrobacter freundii
Enterobacter cloacae
Morganella morganii
Pseudomonas aeruginosa
Serratia marcescens
Stenotrophomonas maltophilia

Other microorganisms
Chlamydia spp.
Chlamydophila spp.
Legionella pneumophila
Mycoplasma spp.
Ureaplasma urealyticum

* No current data were available when the table was published. Sensitivity is assumed in the primary literature, standard works and therapy recommendations.

† The resistance rate is above 50% in at least one region.

§ Collective name for a heterogeneous group of Streptococcus species. Resistance rate can vary depending on the Streptococcus species concerned.

∞ No recent data available; in studies (older than 5 years) the proportion of resistant strains is reported as ≥10%.

The resistance rate is <10% in the outpatient setting.

5.2 Pharmacokinetic properties
High serum levels are reached both after intravenous and intramuscular administration of ampicillin / sulbactam. The results of pharmacokinetic studies in volunteers show the serum concentrations listed in the table in dependence on time, dose and route of administration:

<table>
<thead>
<tr>
<th>Route of admin.</th>
<th>Dose</th>
<th>15 min</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>8 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. m.</td>
<td>0.25 g sulb.†</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0.3</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>0.5 g amp.</td>
<td>9</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>i. m.</td>
<td>0.5 g sulb.†</td>
<td>8</td>
<td>11</td>
<td>12</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td>1 g amp.</td>
<td>10</td>
<td>16</td>
<td>17</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>i. v.</td>
<td>0.5 g sulb.†</td>
<td>21</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>0.4</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>1 g amp.</td>
<td>39</td>
<td>28</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td>i. v.</td>
<td>1 g sulb.†</td>
<td>51</td>
<td>37</td>
<td>21</td>
<td>9</td>
<td>2</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>2 g amp.</td>
<td>95</td>
<td>65</td>
<td>33</td>
<td>12</td>
<td>3</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Mean serum concentrations (mg / l)

Higher peak serum levels are achieved with intravenous administration than with intramuscular administration of ampicillin / sulbactam; the bioavailability of ampicillin / sulbactam is practically complete after intramuscular administration.

Ampicillin and sulbactam are also rapidly distributed to a large number of tissues, body fluids and secretions.

The half-life both of sulbactam and ampicillin is about 1 hour in young adults and about 2 hours in elderly subjects. About 80 % of both substances is excreted renally 8 hours after administration of a single dose of ampicillin / sulbactam. The simultaneous administration of sulbactam and ampicillin...
causes no clinically relevant deviations in the kinetic parameters of the two substances when
administered individually.

5.3 Preclinical safety data
Pre-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose
toxicity and genotoxicity. Long-term studies to evaluate the carcinogenic potential have not been
performed. In studies performed on rats and rabbits at doses up to ten times the human dose, the
combination of ampicillin and sulbactam was not teratogenic and did not have any adverse effects on
fertility (rat).

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal product except those mentioned in
section 6.6.
The following active substances or solutions for reconstitution/dilution should not be administered
simultaneously:
- Ampicillin / Sulbactam should not be mixed together with blood constituents or protein-containing solutions.
- Because of a chemical incompatibility between penicillins and aminoglycosides, which causes
  inactivation of aminoglycosides, Ampicillin / Sulbactam should not be mixed with aminoglycosides in a syringe or infusion solution. The two substances should be administered at different sites at a time interval of at least one hour.
- Another antibiotic (e.g. aminoglycosides).
- The following are also incompatible and should therefore be administered separately:
  metronidazole; injectable tetracycline derivatives such as oxytetracycline, rolitetracycline and
doxycycline; also thiopental sodium; prednisolone; procaine 2%; suxamethonium chloride
  and noradrenaline. Visible signs of incompatibility are precipitation, turbidity or discoloration.

6.3 Shelf life
Unopened vial
2 years.

After opening
The content of the vial should be used immediately after the first breakage of vial.

Reconstituted/Diluted solution
The solution for intramuscular or intravenous injection/infusion must be used immediately after
reconstitution.

From a microbiological point of view, the product should be used immediately. If not used
immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage
Unopened vial: Do not store above 25°C.
For storage conditions after reconstitution/dilution of the medicinal product, see Section 6.3.

6.5 Nature and contents of container
20 ml vial with clear, colourless Type I glass with dark grey bromobutyl rubber stopper. Ampicillin /
Sulbactam 1 g/0.5 g (vial with 1610 mg powder):
Hospital pack with 1 vial.

6.6 Special precautions for disposal
If an injection or infusion solution is to be prepared, this should be performed by trained healthcare
personnel under aseptic conditions in a designated aseptic area.

Intramuscular injection
Dissolve the contents of one vial of Ampicillin / Sulbactam 1 g/0.5 g in 3.2 ml water for injections. To
prevent pain during the injection, the solution can be prepared using 5 mg/ml (0.5%) lidocaine
hydrochloride solution.
Intravenous injection
For intravenous injection, the contents of one vial of Ampicillin / Sulbactam 1 g/0.5 g can be prepared with at least 3.2 ml of water for injections and injected intravenously over at least 3 minutes after the substance has completely dissolved.

Short intravenous infusion
As for the intravenous injection, dissolve the contents of one vial of Ampicillin / Sulbactam 1 g/0.5 g in water for injections and then dilute further with 50 to 100 ml of one of the following infusion solutions: 9mg/ml (0,9%) Sodium Chloride Injection, 50mg/ml (5%) Glucose Injection, Lactated Ringer's Solution, 50mg/ml (5%) Glucose in 0.45% NaCl, 100mg/ml (10%) Invert Sugar. Infuse the finished solution intravenously over 15 to 30 minutes.

The reconstitution/dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solutions is clear and free form particles.

For single use only. Discard any unused solution.
1 NAME OF THE MEDICINAL PRODUCT
Ampicillin / Sulbactam 2 g/1 g Powder for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Active substances: sulbactam sodium, ampicillin sodium

Ampicillin / Sulbactam 2 g/1 g:
Each vial with 3220 mg powder contains 1094 mg sulbactam sodium, equivalent to 1 g sulbactam, and 2126 mg ampicillin sodium, equivalent to 2 g ampicillin.
Excipient: 10 mmol (230 mg) of sodium/vial of powder for solution for injection or infusion.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Powder for solution for injection or infusion
White to off-white powder

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Ampicillin / Sulbactam is indicated in the treatment of the following:
- community acquired pneumonia
- upper urinary tract infection
- intra-abdominal infections
- gynaecological infections (see section 5.1)
- skin and soft tissues infections
- Prophylaxis against infections associated with abdominal surgery.

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

4.2 Posology and method of administration

Posology
The recommended dose for adults is 3 to 12 g Ampicillin / Sulbactam depending on the severity of the infection divided into equal single doses every 6 to 8 hours.

Paediatric patients:
For children over 2 years the recommended dose is 150 mg/kg/day (ampicillin 100 mg/kg/day + sulbactam 50 mg/kg/day). The therapeutic dosage should be given in three or four divided doses.

The intramuscular application should not be given in newborn infants, infants and toddlers (below 2 years). Ampicillin / Sulbactam should be given exclusively by intravenous use according to the following indications:
- For newborn infants above the second living week, infants and toddlers till 2 years the recommended dose is 150 mg/kg/day (ampicillin 100 mg/kg/day + sulbactam 50 mg/kg/day). The therapeutic dosage should be given in three or four divided doses.
- For newborn infants in the first living-week the recommended dose is 75 mg/kg /day (equivalent to ampicillin 50 mg/kg/day plus sulbactam 25 mg/kg/day). The therapeutic dosage should be given in two divided doses.

Use in the Elderly: Ampicillin / Sulbactam injection may be administered in the elderly in the usual dosages with no special precautions.

Prophylaxis of surgical infections: 1.5 - 3g of Ampicillin / Sulbactam injection should be given at induction of anaesthesia, which allows time to achieve effective serum and tissue concentrations during the procedure. In case of long-term surgery another dose in 3-4 hours may be administered. Administration of Ampicillin / Sulbactam is usually stopped 24 hours after the majority of surgical procedures unless a therapeutic course of is indicated.

Use in patients with renal impairment:
In patients with severe renal impairment (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 whatever the renal function is. The dose of Ampicillin / Sulbactam in such patients
should be administered less frequently in accordance with the usual practice for ampicillin.

Recommended dosages for patients with impaired renal function:

<table>
<thead>
<tr>
<th>Creatinine clearance (ml / min)</th>
<th>Dose interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30</td>
<td>6 to 8 hours</td>
</tr>
<tr>
<td>15 to 30</td>
<td>12 hours</td>
</tr>
<tr>
<td>5 to 14</td>
<td>24 hours</td>
</tr>
<tr>
<td>&lt;5</td>
<td>48 hours</td>
</tr>
</tbody>
</table>

Sulbactam and ampicillin are both eliminated from the blood stream to an equal extent by hemodialysis treatment. Ampicillin / Sulbactam should therefore be administered immediately after dialysis and then at 48 hour intervals until the following dialysis treatment.

Use in patients with hepatic impairment: Usual recommended doses.

Method of administration
Please refer to section 6.6.

Duration of use
The duration of treatment depends on the course of the illness. The duration of treatment is generally 5 to 14 days depending on the severity of the infection. In severe cases, treatment may be continued for a prolonged period. The treatment should be continued for another 48 hours after the fever and other symptoms of the disease have subsided.

4.3 Contraindications
Hypersensitivity to the active substances, (ampicillin and sulbactam); to any other penicillin or to any of the excipients listed in section 6.1.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

4.4 Special warnings and precautions for use
Before initiating therapy with ampicillin/sulbactam, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta- lactam agents.

Severe and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin or cephalosporins hypersensitivity and in atopic individuals. If an allergic reaction occurs, ampicillin/sulbactam therapy must be discontinued and appropriate alternative 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.

Before starting a treatment with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins and other drugs.

Ampicillin/sulbactam should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy (more than 14 days). The monitoring is very important in neonates, and in the other paediatric patients.

As with every antibiotic therapy, the physician should be alert to signs of overgrowth of non- sensitive organisms (including fungi). As soon as an infection with these organisms occurs, the product should be discontinued and / or suitable treatment instituted.

Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

During treatment with Ampicillin / Sulbactam, enzymatic glucose oxidase methods should be used
whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

Administration of ampicillin may reduce the efficacy of oral contraceptives. Supplemental non-hormonal contraceptive measures may be required.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including ampicillin / sulbactam and may range in severity from mild to life threatening (see section 4.8). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, Ampicillin / Sulbactam should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation.

Ampicillin / Sulbactam 2 g/1 g: This medicinal product contains 10 mmol (230 mg) of sodium/vial of powder for solution for injection or infusion. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Effects of other medicinal products:

Acetylsalicylic acid, indometacin and phenylbutazone decrease excretion of penicillins.

Other antibiotics or chemotherapeutic agents

Ampicillin / sulbactam should not be combined with bacteriostatic chemotherapeutics or antibiotics such as tetracyclines, erythromycin, sulphonamides or chloramphenicol due to the possibility of reduced effectiveness.

Aminoglycosides are inactivated in vitro by ampicillin: therefore the mixing of aminoglycosides with ampicillin and sulbactam must be avoided in the solution for infusion. If concomitant treatment is necessary the two substances should be administered at different sites at a time interval of at least one hour. (see section 6.2)

Allopurinol
In gout patients being treated with allopurinol, simultaneous treatment with ampicillin / sulbactam increases the likelihood of cutaneous reactions.

Anticoagulants
The changes in platelet aggregation and prothrombin time observed with parenterally administered penicillins may be increased on simultaneous administration of anticoagulants.

Methotrexate
The concurrent administration of methotrexate and penicillins resulted in reduced methotrexate clearance and consequentially in methotrexate toxicity. These patients should be closely monitored and the increased and prolonged administration of Leucovorin should be considered.

Probenecid
The concomitant administration of probenecid leads to higher and more persisting ampicillin and sulbactam concentrations in serum and ampicillin concentrations in the bile due to inhibition of renal elimination (tubular secretion).

Hormonal contraceptives
During treatment with aminopenicillins, the reliability of the contraceptive effect of hormonal contraceptives ("the pill") may be compromised in rare cases. It is therefore recommended to additionally use non-hormonal methods of contraception.

Influence of laboratory tests
A high concentration of ampicillin in urines may result in false positive values of glucosuria. The use of glucose tests based on enzymatic glucose oxydase reactions is recommended.

4.6 Fertility, Pregnancy and lactation

Fertility
In animal studies, ampicillin and sulbactam had no effect on fertility (see section 5.3).
Pregnancy
Data on a limited number of exposed pregnancies indicate no adverse effects of Ampicillin and Sulbactam on pregnancy or on the health of the foetus/newborn child. However, data on first trimester exposure are lacking. In animal studies with ampicillin and sulbactam no teratogenicity was observed (see section 5.3). Ampicillin /Sulbactam should not be used during pregnancy unless clearly necessary.

Lactation
Ampicillin and sulbactam are excreted into human breast-milk. Although excretion of both drugs is low, diarrhoea and fungus infection of the mucous membranes and allergic sensitization could occur in the breast-fed infant. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Ampicillin /Sulbactam should be made taking into account the benefit of breast-feeding to the child and the benefit of Ampicillin / Sulbactam therapy to the woman.

4.7 Effects on ability to drive and use machines
No studies on the ability to drive and use machines under influence of ampicillin and sulbactam have been carried out. However, patients should be made aware that due to undesirable effects (see section 4.8) the reactivity may be decreased.

4.8 Undesirable effects
The following undesirable effects have been observed and reported during treatment with ampicillin / sulbactam with the following frequencies: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data)

The most common undesirable effects are pain at the injection site, phlebitis, nausea, vomiting, meteorism and diarrhea. For severe and persistent diarrhea, the possibility of potentially fatal antibiotic-associated pseudomembranous colitis should be considered. In these cases, Ampicillin / Sulbactam should therefore be discontinued immediately and a suitable therapy (e.g. oral vancomycin 4 x 250 mg daily) instituted. Drugs that inhibit peristalsis are contraindicated.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Frequency</th>
<th>Undesirable effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Not known</td>
<td>Overgrowth of non-sensitive organisms</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very rare</td>
<td>Hematocytological changes such as reversible and haemolytical anemia, thrombocytopenia, eosinophilia and leucopenia. Impairment of blood coagulation.</td>
</tr>
<tr>
<td>Immune system disorders</td>
<td>Rare</td>
<td>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.</td>
</tr>
</tbody>
</table>
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 exsudativum multiforme, Stevens-Johnson syndrome or toxic epidermal necrolysis (Leyell syndrome), 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.

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Uncommon</th>
<th>Vertigo and headache. Neurotoxic reactions (cramps) in events of meningitis or epilepsy, particularly after administration of high doses and impaired renal function respectively.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Common</td>
<td>Nausea, vomiting, meteorism and diarrhoea 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. Peristaltis-inhibiting drugs are contraindicated.</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>Very rare</td>
<td>Transient and reversible increase in transaminases (SGOT [ALT], SGPT [AST]), bilirubinaemia, abnormal liver function tests, jaundice</td>
</tr>
</tbody>
</table>
### Skin and subcutaneous tissue disorders

<table>
<thead>
<tr>
<th>Severity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
<td>Rash, pruritus and other cutaneous 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.</td>
</tr>
</tbody>
</table>

### Musculoskeletal and connective tissue disorders

<table>
<thead>
<tr>
<th>Severity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
<td>Transient and minor increase of creatinephosphokinase (CPK)</td>
</tr>
</tbody>
</table>

### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Severity</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rare</td>
<td>Interstitial Nephritis, crystalluria by high intravenous dosage.</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

#### Very common

- Intramuscular injection may be followed by pain at the injection site.

#### Common

- Intravenous administration may be followed by phlebitis or pain at the injection site.
- Diarrhoea

#### Rare

- As with other parenteral antibiotics, pain at the injection site particularly in connection with an intravenous administration were reported as primary side effects. In some patients phlebitis or reactions in the area of the injection site may occur.
- Asthenia, sleepiness.
- Adverse reactions usually associated with ampicillin alone may also occasionally occur with ampicillin/sulbactam: Arthralgia, stomatitis, black tongue discoloration, agranulocytosis, hereditary angioneurotic edema, exfoliative dermatitis and erythema multiform as well as the occurrence of an anaphylactic shock with a penicillin-hypersensitivity.

### 4.9 Overdose

Only limited experience is available for the acute toxicity of ampicillin / sulbactam. Overdose may induce symptoms corresponding to the undesirable effect profile (see Section 4.8) of Ampicillin / Sulbactam. In such cases, these described undesirable effects may possibly be observed more frequently and in a more severe form. In very high doses, beta-lactam antibiotics can induce cerebral (epileptic) seizures. Since ampicillin and sulbactam can be removed by hemodialysis, in the event of overdose, higher elimination can be achieved by hemodialysis in patients with renal impairment.

**Treatment**

Sedation with diazepam for seizures resulting from overdose.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors, ATC code: J01CR01

Mechanism of action

Ampicillin is a semi-synthetic, non beta-lactamase-resistant aminopenicillin. Sulbactam is a beta-lactamase inhibitor with a structure similar to that of ampicillin and other penicillins.

The mechanism of action of ampicillin is based on inhibition of bacterial wall synthesis (in the growth phase) via blockade of the penicillin-binding proteins (PBPs) such as the transpeptidases. This results in a bactericidal action.

In combination with sulbactam, the inactivation of ampicillin by certain beta-lactamases is inhibited. Sulbactam protects ampicillin from degradation by most beta-lactamases of staphylococci and several plasmid-encoded beta-lactamases (e.g. TEM, OXA) and certain chromosomally encoded beta-lactamases of gram-negative bacteria. These beta-lactamases are present in, for example, *Escherichia coli*, *Klebsiella* spp., *Proteus mirabilis* and *Haemophilus influenzae*. The antibacterial spectrum of action of ampicillin is broadened to include bacteria whose beta-lactamases are inhibited by sulbactam.

PK/PD Relationship

The efficacy depends mainly on the time period for which the active substance level of ampicillin remains above the minimal inhibitory concentration (MIC) of the microorganism.

Mechanisms of resistance

Resistance to ampicillin/sulbactam can be due to the following mechanisms:

- Inactivation by beta-lactamases: ampicillin/sulbactam does not have sufficient activity against beta-lactamase-producing bacteria whose beta-lactamases are not inhibited by sulbactam.
- Reduced affinity of PBPs for ampicillin: the acquired resistance of pneumococci and other streptococci against ampicillin/sulbactam is due to the modification of existing PBPs as the result of a mutation. Meflochlor (oxacillin)-resistant staphylococci are resistant due to the formation of an additional PBP with reduced affinity for ampicillin and all other beta-lactam antibiotics.
- Insufficient penetration of ampicillin through the outer cell wall of gram-negative bacteria can result in inadequate inhibition of the PBPs.
- Ampicillin can be actively extruded from the cell by efflux pumps.

Partial or complete cross-resistance of ampicillin/sulbactam exists with penicillins, cephalosporins and other beta-lactam/beta-lactamase inhibitor combinations.

Breakpoints

MIC breakpoints for Ampicillin / Sulbactam are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Susceptible</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td></td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td><em>Enterococcus spp</em></td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td><em>Haemophilus influenzae</em></td>
<td>≤ 1 mg/l</td>
<td>&gt; 1 mg/l</td>
</tr>
<tr>
<td><em>Moraxella catarrhalis</em></td>
<td>≤ 1 mg/l</td>
<td>&gt; 1 mg/l</td>
</tr>
<tr>
<td><em>Staphylococcus spp</em></td>
<td>≤ 0.12</td>
<td>&gt; 0.12</td>
</tr>
<tr>
<td><em>Streptococcus A, B, C G</em></td>
<td>≤ 0.25</td>
<td>&gt; 0.25</td>
</tr>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>≤ 0.06</td>
<td>&gt; 2</td>
</tr>
<tr>
<td>Gram-negative anaerobes</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
<tr>
<td>Gram-positive anaerobes</td>
<td>≤ 4 mg/l</td>
<td>&gt; 8 mg/l</td>
</tr>
</tbody>
</table>

*Non species-specific limit values*  

1 For susceptibility testing purposes, the concentration of sulbactam is fixed at 4mg/L
2 Susceptibility is inferred from amoxicillin-clavunate
3 Breakpoint values are based on benzylpenicillin breakpoints

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infection is questionable.

Organism susceptibility to ampicillin/sulbactam observed in the European clinical studies conducted...
PAR Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC

in adults or children with various infections have been summarized in the following table.

It must be noted that this information gives only an approximate guidance on the probability that a micro-organism will be susceptible to Ampicillin / Sulbactam.

It must be noted that this information gives only an approximate guidance on the probability that a micro-organism will be susceptible to Ampicillin / Sulbactam.

<table>
<thead>
<tr>
<th>Commonly susceptible species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic gram-positive microorganisms</strong></td>
</tr>
<tr>
<td>Enterococcus faecalis</td>
</tr>
<tr>
<td>Staphylococcus aureus (methicillin-sensitive)</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
</tr>
<tr>
<td>Streptococcus pneumoniae (incl. penicillin-intermediate strains)</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
</tr>
<tr>
<td>Streptococci of the &quot;Viridans group&quot; ^</td>
</tr>
<tr>
<td><strong>Aerobic gram-negative microorganisms</strong></td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
</tr>
<tr>
<td>Moraxella catarrhalis°</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae°</td>
</tr>
<tr>
<td><strong>Anaerobic microorganisms</strong></td>
</tr>
<tr>
<td>Bacteroides fragilis°</td>
</tr>
<tr>
<td>Fusobacterium nucleatum°</td>
</tr>
<tr>
<td>Prevotella spp.</td>
</tr>
<tr>
<td><strong>Other microorganisms</strong></td>
</tr>
<tr>
<td>Gardnerella vaginalis°</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Species for which acquired resistance may be a problem</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aerobic gram-positive microorganisms</strong></td>
</tr>
<tr>
<td>Enterococcus faecium+</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
</tr>
<tr>
<td>Staphylococcus epidermidis+</td>
</tr>
<tr>
<td>Staphylococcus haemolyticus+</td>
</tr>
<tr>
<td>Staphylococcus hominis+</td>
</tr>
<tr>
<td><strong>Aerobic gram-negative microorganisms</strong></td>
</tr>
<tr>
<td>Escherichia coli</td>
</tr>
<tr>
<td>Klebsiella oxytoca</td>
</tr>
<tr>
<td>Klebsiella pneumoniae</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
</tr>
<tr>
<td>Proteus vulgaris</td>
</tr>
</tbody>
</table>

| Inherently resistant organisms Aerobic                            |
gram-positive microorganisms
*Staphylococcus aureus (methicillin-resistant)*

Aerobic gram-negative microorganisms
*Acinetobacter baumannii*
*Citrobacter freundii*
*Enterobacter cloacae*
*Morganella morganii*
*Pseudomonas aeruginosa*
*Serratia marcescens*
*Stenotrophomonas maltophilia*

Other microorganisms
*Chlamydia spp.*
*Chlamydophila spp.*
*Legionella pneumophila*
*Mycoplasma spp.*
*Ureaplasma urealyticum*

° No current data were available when the table was published. Sensitivity is assumed in the primary literature, standard works and therapy recommendations.
+ The resistance rate is above 50% in at least one region.
^ Collective name for a heterogeneous group of Streptococcus species. Resistance rate can vary depending on the Streptococcus species concerned.
∞ No recent data available; in studies (older than 5 years) the proportion of resistant strains is reported as \( \geq 10\% \).
The resistance rate is <10% in the outpatient setting.

5.2 Pharmacokinetic properties
High serum levels are reached both after intravenous and intramuscular administration of ampicillin / sulbactam. The results of pharmacokinetic studies in volunteers show the serum concentrations listed in the table below in dependence on time, dose and route of administration:

<table>
<thead>
<tr>
<th>Route of admin.</th>
<th>Dose</th>
<th>15 min</th>
<th>30 min</th>
<th>1 h</th>
<th>2 h</th>
<th>4 h</th>
<th>6 h</th>
<th>8 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. m. 0.25 g sulb.+</td>
<td>6</td>
<td>7</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>0.3</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>i. m. 0.5 g amp.</td>
<td>9</td>
<td>12</td>
<td>12</td>
<td>6</td>
<td>2</td>
<td>0.4</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>i. m. 0.5 g sulb.+</td>
<td>8</td>
<td>11</td>
<td>12</td>
<td>8</td>
<td>3</td>
<td>1</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>i. m. 1 g amp.</td>
<td>10</td>
<td>16</td>
<td>17</td>
<td>13</td>
<td>4</td>
<td>1</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>i. v. 0.5 g sulb.+</td>
<td>21</td>
<td>15</td>
<td>9</td>
<td>4</td>
<td>1</td>
<td>0.4</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>i. v. 1 g amp.</td>
<td>39</td>
<td>28</td>
<td>14</td>
<td>6</td>
<td>1</td>
<td>0.4</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>i. v. 1 g sulb.+</td>
<td>51</td>
<td>37</td>
<td>21</td>
<td>9</td>
<td>2</td>
<td>0.7</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>i. v. 2 g amp.</td>
<td>95</td>
<td>65</td>
<td>33</td>
<td>12</td>
<td>3</td>
<td>1</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

Mean serum concentrations (mg / l)

Higher peak serum levels are achieved with intravenous administration than with intramuscular administration of ampicillin / sulbactam; the bioavailability of ampicillin / sulbactam is practically complete after intramuscular administration.

Ampicillin and sulbactam are also rapidly distributed to a large number of tissues, body fluids and secretions.

The half-life both of sulbactam and ampicillin is about 1 hour in young adults and about 2 hours in
PAR Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC

elderly subjects. About 80 % of both substances is excreted renally 8 hours after administration of a single dose of ampicillin / sulbactam. The simultaneous administration of sulbactam and ampicillin causes no clinically relevant deviations in the kinetic parameters of the two substances when administered individually.

5.3 Preclinical safety data
Pre-clinical data reveal no special hazard for humans based on conventional studies of repeated-dose toxicity and genotoxicity. Long-term studies to evaluate the carcinogenic potential have not been performed. In studies performed on rats and rabbits at doses up to ten times the human dose, the combination of ampicillin and sulbactam was not teratogenic and did not have any adverse effects on fertility (rat).

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
None.

6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal product except those mentioned in section 6.6.
The following active substances or solutions for reconstitution/dilution should not be administered simultaneously:
- Ampicillin / Sulbactam should not be mixed together with blood constituents or protein-containing solutions.
- Because of a chemical incompatibility between penicillins and aminoglycosides, which causes inactivation of aminoglycosides, Ampicillin / Sulbactam should not be mixed with aminoglycosides in a syringe or infusion solution. The two substances should be administered at different sites at a time interval of at least one hour.
- Another antibiotic (e.g. aminoglycosides).
The following are also incompatible and should therefore be administered separately: metronidazole; injectable tetracycline derivatives such as oxytetracycline, rolitetracycline and doxycycline; also thiopental sodium; prednisolone; procaine 2 %; suxamethonium chloride and noradrenaline. Visible signs of incompatibility are precipitation, turbidity or discoloration.

6.3 Shelf life
Unopened vial
2 years.

After opening
The content of the vial should be used immediately after the first breakage of vial.

Reconstituted/Diluted solution
The solution for intramuscular or intravenous injection/infusion must be used immediately after reconstitution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage
Unopened vial: Do not store above 25°C.
For storage conditions after reconstitution/dilution of the medicinal product, see Section 6.3.

6.5 Nature and contents of container
20 ml vial with clear, colourless Type I glass with dark grey bromobutyl rubber stopper.
Ampicillin / Sulbactam 2 g/1 g (vial with 3220 mg powder): Hospital pack with 1 vial.

6.6 Special precautions for disposal
If an injection or infusion solution is to be prepared, this should be performed by trained healthcare personnel under aseptic conditions in a designated aseptic area.
Intramuscular injection
Dissolve the contents of one vial of Ampicillin / Sulbactam 2 g/1 g in 6.4 ml water for injections. To prevent pain during the injection, the solution can be prepared using 5 mg/ml (0.5%) lidocaine hydrochloride solution.
Intravenous injection
For intravenous injection, the contents of one vial of Ampicillin / Sulbactam 2 g/1 g can be prepared with at least 6.4 ml of water for injections and injected intravenously over at least 3 minutes after the substance has completely dissolved.

Short intravenous infusion
As for the intravenous injection, dissolve the contents of one vial of Ampicillin / Sulbactam 2 g/1 g in water for injections and then dilute further with 100 ml of one of the following infusion solutions: 9mg/ml (0.9%) Sodium Chloride Injection, 50mg/ml (5%) Glucose Injection, Lactated Ringer’s Solution, 50mg/ml (5%) Glucose in 0.45% NaCl, 100mg/ml (10%) Invert Sugar. Infuse the finished solution intravenously over 15 to 30 minutes.

The reconstitution/dilution is to be made under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solutions is clear and free from particles.

For single use only. Discard any unused solution.

MARKETING AUTHORISATION HOLDER
Strides Arcolab International Limited
Unit 4, Metro Centre,
Tolpits Lane, Watford,
Herts, WD18 9SS
United Kingdom

MARKETING AUTHORISATION NUMBER(S)
PL 28176/0048

DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/07/2012

DATE OF REVISION OF THE TEXT
02/07/2012
PAR Ampicillin/Sublactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion

UK/H/4322/001-2/DC

Module 3

The following information is intended for healthcare professionals

Medication

Duration of use

2 years

After opening
The content of the vial should be used immediately after the

Reconstituted/Dispensed solution

The solution for intravenous or intramuscular injection/infiltration

should be used immediately after preparation.

From a microbiological point of view, the product should be

used immediately after dilution. No storage is possible.

Information for prescriber and patient

If an injection or infusion solution is to be prepared, this should be
performed by trained healthcare personnel under aseptic conditions:

Intravenous injection

Dissolve the contents of one vial of Ampicillin Sublactam 1 or 2 ml of water for injection. To prevent pain during the infusion, add 5 ml of 0.9% sodium chloride by solution.

Intramuscular injection

For intramuscular injection, the contents of one vial of Ampicillin Sublactam 1 or 2 ml of water for injection are injected intramuscularly over at least 3 minutes after the commencement of the injection.

Short infusion solution

As for the intravenous injection, dissolve the contents of one vial of Ampicillin Sublactam 1 or 2 ml of water for injection and inject intravenously with the following solutions in 10 ml of one of the following infusion solutions:

- 0.9% Sodium Chloride Injection
- 5% Glucose Injection
- 5% Glucose in 0.9% Sodium Chloride Injection
- 10% Glucose Injection
- 10% Glucose in 0.9% Sodium Chloride Injection

The reconstituted solution is to be made under aseptic conditions as the product is ready for administration. The solution should be used only if clear and free from particulate matters.

For single use only. Discard any unused solution.

If you are given more Ampicillin Sublactam 1 g/0.5 g than you should

It is unlikely you will be given too much, but if you think you have been given too much
PAR Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC

Ampicillin/Sulbactam tell your doctor, pharmacist or nurse immediately. Signs may be an
unusual taste, infrequent bowel movements, loss of appetite, nausea, vomiting, diarrhea, or
fatigue.

If you have any further questions about how this product is given, ask your doctor, pharmacist or
nurse.

4. POSSIBLE SIDE EFFECTS
Like all medicines, this medicine can cause side effects, although not everybody gets them.
Conditions you need to look out for:

Allergic reactions:
- skin rash
- inflammation of blood vessels (vasculitis) which may be visible as red or purple spots
  on the skin, but can affect other parts of the body
- fever, joint pain, swollen glands in the neck, armpit or groin
- swelling, sometimes of the face or mouth (angioedema), coughing difficulty in breathing
- collapse.

Contact a doctor immediately if you get any of these symptoms. Stop taking Ampicillin
/Sulbactam.

Inflammation of large intestine
Inflammation of the large intestine, causing watery diarrhea usually with blood and mucus,
stomach pain and/or fever.

Contact your doctor as soon as possible for advice if you get these symptoms.

The possible side effects are listed according to the following categories:

"Very common" means that the side effect occurs in 1 or more users in a group of
10 users.

"Common" means that the side effect occurs in 1 to 10 of 100 users.

"Uncommon" means that the side effect occurs in 1 to 10 of 1,000 users.

"Rare" means that the side effect occurs in fewer than 1 of 1,000 users.

"Very rare" means that the side effect occurs in fewer than 1 of 10,000 users.

"Not known" means that the frequency cannot be estimated from the available
data.

Very common side effects:
- Pain at the injection site with the intramuscular route of administration.

Common side effects:
- Pain at the injection site with the intravenous route of administration.
- Inflammation at the site of injection or infusion.

Uncommon side effects:

Skin rashes
- itch
- dermatitis and other non-specific skin reactions
- weakness
- sleepiness
- dizziness
- headache
- cramps

Rare side effects:
- kidney inflammation (interstitial nephritis)
- presence of crystals in the urine

Very rare side effects:
- Allergic reaction of red blood cells (anemia)
- alteration of the number of white blood cells
- lowering of blood platelets with alteration of coagulation mechanisms
- increasing of the creatinine phosphokinase (CPK)
- liver disorders
- abnormal liver function tests (transaminases, aspartate and alanine transaminase increase)
- jaundice

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side
effects not listed in this leaflet.

5. HOW TO STORE AMPICILLIN / SULBACTAM 1 g/0.5 g
Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the label after
"EXP" The expiry date refers to the last day of the month.

Storage conditions:
Unopened vial.
Do not store above 25°C.
Reconstituted/Diluted solution:
The solution for intramuscular or intravenous injection must be used immediately after
reconstitution.

Medicines should not be disposed of via wastewater or household waste. Ask your
pharmacist how to dispose of medicines no longer required. These measures will help to protect
the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION
What Ampicillin / Sulbactam 1 g/0.5 g contains
- The active substances are sulbactam sodium and ampicillin sodium.

Each vial with 290 mg powder contains 145 mg sulbactam sodium, equivalent to 0.5 g
sulbactam, and 146 mg ampicillin sodium, equivalent to 1 g ampicillin.

There are no other ingredients.

What Ampicillin / Sulbactam 1 g/0.5 g looks like and contents of the pack
Ampicillin / Sulbactam 1 g/0.5 g is a white to off-white powder for solution for injection or
infusion in a vial of clear, colorless glass.

Hospital pack with 1 vial with 1400 mg powder.

Marketing Authorisation Holder
Strides Acrolab International Limited
Unit 4, Matta Court, Tophil Lane, Wiltford, Ets. WS19 5RS United Kingdom.

Manufacturer:
Strides Acrolab Polska Sp z o o
10, Dusaniewska St.,
02-530 Warsaw, Poland

This medicinal product is authorised in the Member States of the EEA under the following
numbers:

United Kingdom: Amoxicillin/Sulbactam;
Germany: Amoxicillin / Sulbactam Strides;
Austria: Amoxicillin / Sulbactam Strides;
Italy: Amoxicillin / Sulbactam Strides Acrilab International;
Czech Republic: Amoxicillin / Sulbactam Strides;
Poland: Amoxicillin / Sulbactam Strides;
Belgium: Amoxicillin / Sulbactam Strides;
Slovak Republic: Amoxicillin / Sulbactam Strides;

This leaflet was last revised in 06/2012.
PAR Ampicillin/Subactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC

1. WHAT AMPICILLIN/SUBLACTAM 2 G/1 G POWDER {AND WHAT IT IS USED FOR}:
Ampicillin / Subactam 2 g/1 g is an antibacterial and anti-pyretic drug that can be used in the treatment of various infections. It contains two different antibiotics, Ampicillin and Subactam, which work together to treat different types of infections.

2. POSSIBLE SIDE EFFECTS:
Ampicillin / Subactam may cause some side effects. These include:
- Nausea
- Vomiting
- Diarrhea
- Rash
- Headache
- Shivering
- Blood in stools

3. HOW TO STORE AMPICILLIN/SUBLACTAM 2 G/1 G POWDER:
Store the drug in a cool, dry place away from direct sunlight. Do not store in the bathroom or kitchen.

4. COMMON DRUGS AND THEIR USES:
- Ampicillin / Subactam 2 g/1 g can be used to treat infections caused by bacteria.
- Ampicillin / Subactam 1 g/0.5 g can be used to treat infections caused by viruses.

5. DRIVING AND USING MACHINERY:
Ampicillin / Subactam does not affect your ability to drive, but it can cause some side effects such as dizziness, which may affect your ability to perform certain tasks.

6. ADVICE BEFORE YOU TAKE AMPICILLIN/SUBLACTAM 2 G/1 G POWDER:
Before taking Ampicillin / Subactam, you should tell your doctor about any other medications you are taking, any allergies, and any other conditions you have.

7. STEPS TO TAKE BEFORE YOU TAKE AMPICILLIN/SUBLACTAM 2 G/1 G POWDER:
- Wash your hands before taking the drug.
- Take the drug with food to reduce any stomach upset.

8. DURATION OF TREATMENT:
The duration of treatment will depend on the severity of the infection. You should complete the full course of the medication as prescribed by your doctor.

9. DISPOSAL OF AMOUNTED MEDICATION:
Do not dispose of medication in the toilet or sink. Instead, return any unneeded medication to the pharmacist or local pharmacy.

10. UNPACKING INSTRUCTIONS:
Ensure that the vial is unbroken and the drug is not past its expiration date.

11. AFTER USE:
Wash your hands after using the drug.

12. OTHER IMPORTANT INFORMATION:
- Ampicillin / Subactam can cause allergic reactions in some people.
- If you experience any side effects, stop taking the drug and consult your doctor.

13. HEALTH AND SAFETY INSTRUCTIONS:
- Store Ampicillin / Subactam in a cool, dry place away from direct sunlight.
- Keep out of reach of children.

14. LEGAL INFORMATION:
Ampicillin / Subactam is a prescription-only medication.

15. ADDITIONAL INFORMATION:
For more information, contact your doctor or pharmacist.

16. IMPORTANT INFORMATION:
Read the full instruction sheet that comes with the drug before using it.

17. CONTRAINDICATIONS:
Ampicillin / Subactam is contraindicated in patients with a history of allergy to penicillins.

18. DOSAGE AND ADMINISTRATION:
Follow the dosage instructions provided by your doctor. The usual dosage is 250 mg to 1 g every 6 to 8 hours.

19. ADVERSE REACTIONS:
Common side effects include nausea, vomiting, diarrhea, and allergic reactions.

20. CLINICAL PHARMACOLOGY:
Ampicillin / Subactam is a combination of two antibiotics that work together to treat infections.

21. PHARMACOKINETICS:
Absorption is rapid and complete. Peak plasma levels are achieved in 1 to 2 hours.

22. INTERACTIONS:
Ampicillin / Subactam may interact with other medications. Consult your doctor or pharmacist for guidance.

23. STORAGE:
Store at room temperature in a cool, dry place away from direct sunlight.

24. PRECAUTIONS:
Use Ampicillin / Subactam as directed by your doctor.

25. PATIENT INFORMATION:
Read the full instruction sheet before using Ampicillin / Subactam.

26. PATIENTS' INFORMATION:
Before using Ampicillin / Subactam, read the full instruction sheet.

27. PRODUCT INFORMATION:
For more information, contact your doctor or pharmacist.

28. PACKAGE LEAFLET INFORMATION:
For complete information, contact your doctor or pharmacist.

29. MEDICAL INFORMATION:
For medical advice, contact your doctor or pharmacist.

30. PATIENT'S INFORMATION:
Read the full instruction sheet before using Ampicillin / Subactam.
PAR Ampicillin/Sublactam 1g/0.5g and 2g/1g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC

4. POSSIBLE SIDE EFFECTS
Like all medicines, this medicine can cause side effects, although not everybody gets them.
Conditions you need to look out for
Allergic reactions:
• skin rash
• inflammation of blood vessels (vasculitis) which may be visible as red or purple raised spots on the skin, but can affect other parts of the body
• fever, joint pain, swollen glands in the neck, smart or groin
• swelling, sometimes of the face or mouth (angioedema), causing difficulty in breathing
• collapse.

Contact a doctor immediately if you get any of these symptoms. Stop taking Ampicillin / Sublactam.
Inflammation of large intestine
Inflammation of the large intestine, causing watery diarrhoea usually with blood and mucus, stomach pain and/or fever.
Contact your doctor as soon as possible for advice if you get these symptoms.
The possible side effects are listed according to the following categories:

"Very common" means that the side effect occurs in 1 or more users in a group of 10 users.
"Common" means that the side effect occurs in 1 to 10 users.
"Uncommon" means that the side effect occurs in 1 to 10,000 users.
"Rare" means that the side effect occurs in fewer than 1 of 1,000 users.
"Very rare" means that the frequency cannot be estimated from the available data.

Very common side effects:
• Pain at the injection site with the intramuscular route of administration.

Common side effects:
• Pain at the injection site with the intravenous route of administration
• Inflammation of a vein after intravenous administration
• Nausea
• Vomiting
• Nausea
• Diarrhoea
• Headache
• Rash
• Itching
• Dizziness
• Night sweats
• Rash
• Diaphoresis

Uncommon side effects:
• Skin
• Rash
• Itch
• Dermatitis and other non-specific skin reactions
• Weakness
• Sleepiness
• Dizziness
• Headache
• Constipation

Rare side effects:
• Kidney inflammation (interstitial nephritis)
• Presence of crystals in the urine

Very rare side effects:
• Alteration of red blood cells (anaemia)
• Alteration of the number of white blood cells
• Lowering of blood platelets with alteration of coagulation mechanism

• Altering of the creatinine phosphokinase (CPK)
• Liver disorders
• Abnormal liver function tests (transaminases, leucinase and creatinine increase)
• Jaundice
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any side effects not listed in this leaflet.

5. HOW TO STORE AMpicillin / SUBlactam 2 g/1 g
Keep this medicine out of the sight of and reach of children.
Do not use this medicine after the expiry date which is stated on the canister and the label after "EXP": The expiry date refers to the last day of the month.

Storage conditions:
Unopened vial:
Do not store above 25°C.

Reconstituted / Diluted solution:
The solution for intramuscular or intravenous injection must be used immediately after reconstitution.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. CONTENTS OF THE PACK AND OTHER INFORMATION
What Ampicillin / Sublactam 2g/1g contains:
- The active substances are sublactam sodium and ampicillin sodium. Each vial with 3220 mg powder contains 1094 mg sublactam sodium, equivalent to 1 g sublactam, and 2126 mg ampicillin sodium, equivalent to 2 g ampicillin.

There are no other ingredients.

What Ampicillin / Sublactam 2g/1g looks like and contents of the pack:
Ampicillin / Sublactam 2 g/1 g is a white to off-white powder for solution for injection or infusion in a vial of clear, colourless glass.
Hospital pack with 1 vial with 3220 mg powder.

Marketing Authorization Holder:
Strides Arcelab International Limited
Unit 4, Metro Centre,
Tolpits Lane, Watford,
Herts,
WD18 9SS
United Kingdom

Manufacturer:
Strides Arcelab Polska Sp. z o.o
10, Dziennecka Str.,
03-250 Warsaw,
Poland

This medicinal product is authorised in the Member States of the EEA under the following names:
United Kingdom: Ampicillin/Sublactam
Germany: Ampicillin / Sublactam Strides
Austria: Ampicillin & Sublactam Strides
Italy: Ampicillin & Sublactam Strides Arcelab International
Czech Republic: Ampicillin/Sublactam Strides
Poland: Ampicillin & Sublactam Strides
Bulgaria: Ampicillin & Sublactam Strides
Slovak Republic: Ampicillin & Sublactam Strides

This leaflet was last revised in 06/2012.
Module 4

Labelling

Each vial contains: 1 g Amoxicillin (as Amoxicillin sodium) and 0.5 g Sulbactam (as Sulbactam sodium)
Contains Sodium. Please refer to the package leaflet before use.
Reconstituted/diluted solution should be used immediately.
For single use only. Discard any remaining solution.
Keep out of the sight and reach of children.
For storage conditions and in use shelf-life of the reconstituted/diluted product see package leaflet.
Do not store above 25°C.

Strides Arcelab International Limited
Unit 4, Metro Centre, Toiptis Lane, Watford,
Herts, WD18 9SS, United Kingdom.
BN
EXP

PL 28176/0047
Medicinal product subject to medical prescription.

PL 28176/0047
POM

Barcode @ 80%

34 x 34 x 65 mm
PAR Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC
Each vial contains: 2 g Ampicillin (as Ampicillin sodium) and 1 g Sulbactam (as Sulbactam sodium).

Contains Sodium. Please refer to the package leaflet before use.

Reconstituted/diluted solution should be used immediately.

For single use only. Discard any remaining solution.

Keep out of the sight and reach of children.

For storage conditions and in-use shelf-life of the reconstituted/diluted product, see the package leaflet. Do not store above 25°C.

Code No.: K5VDRUGS/K7K/28/307/99

Strides Arcadab International Limited
Unit 4, Metro Centre, Tolpits Lane, Watford,
Herts, WD18 9SS, United Kingdom.

BN EXP PL 28176/0048

Medical product subject to medical prescription.
Module 5
Scientific discussion during initial procedure

I  INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the applications for Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion in the treatment of bacterial infections could be approved.

These applications were submitted under Article 10.1, claiming to be generic medicinal products of Unasyn Injection 1500, 1.5 g and Unasyn 3000, 3 g powder for injection (PL 00057/0248-9), which were first licensed in the UK to Pfizer Limited, on 27th August 1985.

With UK as the RMS in these Decentralised Procedures (UK/H/4322/001-2/DC), Strides Arcolab International Limited applied for the Marketing Authorisations for Ampicillin / Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion in the following CMSs:

Austria, Bulgaria, Czech, Republic, Germany, Italy, Poland and Slovak Republic.

Ampicillin/Sulbactam powder for solution for injection or infusion is an injectable antibacterial combination consisting of ampicillin sodium and sulbactam sodium. Ampicillin is a semi-synthetic, non beta-lactamase-resistant aminopenicillin. Sulbactam is a beta-lactamase inhibitor with a structure similar to that of ampicillin and other penicillins.

The mechanism of action of ampicillin is based on inhibition of bacterial wall synthesis via blockade of the penicillin-binding proteins (PBPs) resulting in a bactericidal action.

In combination with sulbactam, the inactivation of ampicillin by certain beta-lactamases is inhibited. Sulbactam protects ampicillin from degradation by most beta-lactamases of staphylococci and several plasmid-encoded beta-lactamases (e.g. TEM, OXA) and certain chromosomally encoded beta-lactamases of gram-negative bacteria. These beta-lactamases are present in, for example, Escherichia coli, Klebsiella spp., Proteus mirabilis and Haemophilus influenzae. The antibacterial spectrum of action of ampicillin is broadened to include bacteria that are inhibited by sulbactam.

No new clinical or non-clinical studies were conducted, which is acceptable given that the applications were based on being generic medicinal products of the originator products that have been licensed for over 10 years. Bioequivalence studies are not necessary to support these applications for parenteral products.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of these products. For manufacturing sites outside the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS considers that the Pharmacovigilance System as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the
PAR Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC
notification of any adverse reaction suspected of occurring either in the Community or in a third country. A suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licences for the above products at the end of procedure (Day 210 – 24th May 2012). After a subsequent national phase, the UK granted licences for these products on 2nd July 2012 (PL 28176/0047-8).
### II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g Powder for Solution for Injection or Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the active substance(s) (USAN)</td>
<td>Ampicillin sodium</td>
</tr>
<tr>
<td></td>
<td>Sulbactam sodium</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Combinations of penicillins, incl. beta-lactamase inhibitors, ATC code: J01CR01</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>Powder for Solution for Injection or Infusion</td>
</tr>
<tr>
<td></td>
<td>1 g or 2 g Ampicillin Sodium</td>
</tr>
<tr>
<td></td>
<td>0.5 g or 1 g Sulbactam sodium</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4322/001-2/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Concerned Member States</td>
<td>Austria, Bulgaria, Czech Republic, Germany, Italy, Poland and Slovak Republic</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 28176/0047-8</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Strides Arcolab International Limited, Unit 4, Metro Centre, Tolpits Lane, Watford, Hertfordshire, WD 189 SS, UK</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Ampicillin sodium

Chemical Names: Sodium (2S,5R,6R)-6-[(2R)-2-amino-2-phenylacetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate

Structure:

![Ampicillin Sodium Structure](image1)

Molecular formula: C_{16}H_{18}N_{3}NaO_{4}S

Molecular weight: 371.4

Physical form: White or almost white powder, hygroscopic.

Solubility: freely soluble in water, practically insoluble in acetone, in fatty acid and in liquid paraffin.

Ampicillin sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance ampicillin sodium are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

INN: Sulbactam sodium

Chemical Names: Sodium (2S,5R)-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate 4,4-dioxide

Structure:

![Sulbactam Sodium Structure](image2)

Molecular formula: C_{8}H_{10}NNaO_{5}S

Molecular weight: 255.2

Physical form: white or almost white, crystalline powder

Solubility: freely soluble in water, practically insoluble in ethyl acetate and in ethanol (96 %),
PAR Ampicillin/ Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion
UK/H/4322/001-2/DC
freely soluble in diluted acids

Sulbactam sodium is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance sulbactam sodium are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

DRUG PRODUCT
Other Ingredients
There are no excipients present.

Pharmaceutical Development
The objective of the pharmaceutical development programme was to obtain stable products containing ampicillin sodium and sulbactam sodium that could be considered generic medicinal products of Unasyn Injection 1500 1.5 g and 3000 3 g Powder for Injection Powder for Injection (Pfizer Limited).

Suitable pharmaceutical development data have been provided for these applications.

Comparative impurity profiles have been provided for the proposed and originator products.

Manufacture
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on commercial batches have been provided. The results are satisfactory.

Finished Product Specifications
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Container Closure System
The finished product is supplied in a vial with clear, colourless Type I glass with dark grey bromobutyl rubber stopper. The pack sizes are one vial with Ampicillin / Sulbactam 1 g/0.5 g (vial with 1610 mg powder) or 2 g/1 g (vial with 3220 mg powder).

Specifications and Certificates of Analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines.

Stability
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years for unopened vial, with storage condition of “Do not store above 25 °C” have been set.
Reconstituted/Diluted solution
The solution for intramuscular or intravenous injection/infusion must be used immediately after reconstitution.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Bioequivalence/bioavailability
No bioequivalence studies have been submitted and none are required to support an application of this type.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SPCs, PILs and labelling are pharmaceutically satisfactory.

A package leaflet has been submitted to the MHRA together with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

Marketing Authorisation Application (MAA) Forms
The MAA forms are pharmaceutically satisfactory.

Expert Report
A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Post-approval commitment
The applicant commits that the commercial batch samples will be tested to demonstrate the physical and chemical stability in-use stability of the reconstituted/diluted solutions. They also confirm that the agency will be informed immediately in-case any out of specification results are observed with any of the diluents.

Conclusion
There are no objections to the approval of these products from a pharmaceutical point of view.

III.2 NON-CLINICAL ASPECTS
PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY
The pharmacological, pharmacokinetic and toxicological properties of sulbactam sodium and ampicillin sodium are well-known.

No new non-clinical data have been supplied with these applications and none are required for applications of this type. The non-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.
A suitable justification has been provided for non-submission of the environmental risk assessment.

There are no objections to the approval of these products from a non-clinical point of view.

### III.3 CLINICAL ASPECTS

**Pharmacokinetics**

In accordance with Note for Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1), a bioequivalence study is not requested if the test product is an aqueous intravenous solution containing the same active substance as the reference product. No bioequivalence study has been submitted with these applications and none is required.

No new data have been submitted and none are required for applications of this type.

**Pharmacodynamics**

No new data have been submitted and none are required for applications of this type.

**Clinical efficacy**

No new data have been submitted and none are required for applications of this type.

**Clinical safety**

Sulbactam sodium and ampicillin sodium have an acceptable adverse events profile. No new safety data are supplied or required for these generic applications. Sulbactam sodium and ampicillin sodium have a well-established side-effect profile and is generally well-tolerated.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling**

The SmPCs, PILs and labelling are medically satisfactory and consistent with those for the reference products.

**Clinical Expert Report**

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**Marketing Authorisation Application (MAA) Forms**

The MAA forms are medically satisfactory.

**Clinical Conclusion**

There are no objections to the approval of these products from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Ampicillin/Sulbactam 1 g/0.5 g and 2 g/1 g powder for Solution for Injection or Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none were required for applications of this type.

EFFICACY
No new efficacy data were submitted and none were required for applications of this type. As the safety profiles of sulbactam sodium and ampicillin sodium are well-known, no additional data were required. No new or unexpected safety concerns arose from these applications.

The SmPCs, PILs and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with sulbactam sodium and ampicillin sodium is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>