

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name and Dosage form of product

Ampicillin Sodium and Cloxacillin Sodium for Injection 0.5g

2. Qualitative and quantitative composition

250g ampicillin as Ampicillin Sodium with 250mg cloxacillin as Cloxacillin Sodium.

3. Pharmaceutical form

White or almost white powder.

Powder for injection

4. Clinical particulars

4.1. Therapeutic indications

Ampicillin sodium and cloxacillin sodium is indicated for the treatment of infections in which susceptible organisms have been detected or are suspected (see Section 6):

-Surgery: post-operative wound infections, post-operative pulmonary infections

-Respiratory infections: bronchopneumonia, acute exacerbations of chronic bronchitis

-Obstetrics: puerperal fever

-Bacteraemia when associated with, or suspected to be associated with, any of the infections listed in 5.1.

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

4.2. Posology and method of administration

Intramuscular/ Intravenous

Adult dosage (including Elderly):

One to two vials every four to six hours.

Children's dosage:

Up to two years:

Quarter adult dose

Two to Ten years:

Half adult dose.

Dosage may be further increased where necessary.

ADMINISTRATION

500 mg vials

Intramuscular

Dissolve vial contents in 1.5 ml Water for Injections BP.

Intravenous

Dissolve vial contents in 10 ml Water for Injections BP and administer slowly (three to

four minutes). Ampicillin sodium and cloxacillin sodium for Injection may also be added to infusion fluids or injected, suitably diluted, into the drip tube over a period of three to four minutes.

Renal Impairment:

In cases of renal failure, the dosage should be adapted in accordance with the following:

	Dosing recommendation
Creatinine Clearance >50 mL/min	Normal dosing according to indication
Creatinine Clearance 50 to 10 mL/min	Dosage (oral or parenteral administration) initial dose: normal dose according to indication Dosage (oral or parenteral administration) maintenance dose: the normal unit dose (ampicillin-cloxacillin 500 mg orally up to 1 g IM or IV) three times daily
Creatinine Clearance <10 mL/min	Dosage (oral or parenteral administration) initial dose: normal dose according to indication Dosage (oral or parenteral administration) maintenance dose: the normal unit dose twice or once daily
Haemodialysis	In case of dialysis, an additional normal unit dose (ampicillin - cloxacillin 500 mg orally, up to 1 g IM. or IV) is to be administered after the procedure

Hepatic impairment

Reduce frequency of administration depending on the severity of the condition.

4.3. Contra-Indications

Penicillin hypersensitivity; ocular administration. Attention should be paid to possible cross-sensitivity with other beta-lactam antibiotics, e.g. cephalosporins, penicillins.

4.4. Special warnings and precautions for use

Before initiating therapy with ampicillin sodium and cloxacillin sodium for injection, careful enquiry should be made concerning previous hypersensitivity reactions to beta-lactams.

Caution should be observed when administering Ampicillin sodium and cloxacillin sodium for injection to babies whose mothers are hypersensitive to penicillin.

Ampicillin sodium and cloxacillin sodium for injection should be avoided if infectious mononucleosis is suspected.

Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be

discontinued immediately and the patient investigated further.

Dosage should be adjusted in patients with renal impairment (see section 4.2).

Sodium Content

One gram of this medicinal product contains 60 mg of sodium. To be taken into consideration by patients on a controlled sodium diet.

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant use of allopurinol during treatment with ampicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of Ampicillin sodium and cloxacillin sodium and allopurinol.

In common with other antibiotics, Ampicillin sodium and cloxacillin sodium for injection may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives. Therefore, alternative non-hormonal methods of contraception are recommended.

Concurrent use with probenecid may result in increased and prolonged blood levels of Ampicillin sodium and cloxacillin sodium.

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

4.6. Fertility, pregnancy and lactation

Animal studies have shown no teratogenic effects. The product has been in clinical use since 1968 and the limited number of reported cases of use in human pregnancy has shown no evidence of untoward effect. The use of Ampicillin sodium and cloxacillin sodium for injection in pregnancy should be reserved for cases considered essential by the clinician. During lactation, trace quantities of penicillins can be detected in breast milk.

4.7. Effects on ability to drive and use machines

None known.

4.8. Undesirable effects

The following statements reflect the information available on the adverse reaction profile of the individual constituents (ampicillin and cloxacillin for injection) and/or the combination in ampicillin sodium and cloxacillin sodium for injection. The majority of the adverse reactions listed below are not unique to ampicillin sodium and cloxacillin sodium for injection and may occur when using other penicillins.

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as : very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000), including isolated reports. Common and uncommon adverse reactions were generally determined from pooled safety data from a clinical population of 1210 treated patients. Rare and very rare adverse reactions were generally determined from more than 32 years of post-marketing experience data and refer to reporting rate rather than true frequency.

Blood and lymphatic system disorders

Very rare: Haemolytic anaemia, leucopenia, thrombocytopenia and agranulocytosis.

Immune system disorders

Very rare: Anaphylaxis (see item 5.4 Warnings) and other hypersensitive reactions. Skin

disorders and interstitial nephritis have been reported as hypersensitivity reactions. (See also Skin and subcutaneous tissue disorders and Renal and urinary disorders).

If any hypersensitivity reaction occurs, the treatment should be discontinued.

Nervous system disorders

Very rare: Myoclonus and convulsions.

Gastrointestinal disorders

Common: Diarrhoea and nausea.

Uncommon: Vomiting.

Very rare: Pseudomembranous colitis (see 5.4 Warnings and Precautions) and haemorrhagic colitis.

Hepato-biliary disorders

Very rare: Hepatitis and cholestatic jaundice. A moderate and transient increase in transaminases.

Skin and subcutaneous tissue disorders

Common: Skin rash, urticaria and pruritus.

The incidence of skin rash, pruritus and urticaria is higher in patients suffering from infectious mononucleosis and acute or chronic leukaemia of lymphoid origin.

Very rare: Bullous reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), exfoliative dermatitis and purpura.

Skin disorders have also been reported as hypersensitivity reactions (see Immune system disorders)

Renal and urinary disorders

Very rare: Interstitial nephritis.

Interstitial nephritis has also been reported as a hypersensitivity reaction. (See also Immune system disorders)

4.9. Overdose

Overdosage with oral ampicillin - cloxacillin is unlikely to cause serious reactions if renal function is normal. Very high dosage of i.v. administered ampicillin and/or high dosage of cloxacillin in renal failure may provoke neurotoxic reactions similar to those seen with benzylpenicillin in excess. Gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident.

Gastrointestinal effects should be treated symptomatically. Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Penicillins with extended spectrum

ATC code: J01CA51

Ampicillin sodium and cloxacillin sodium for injection is a combination of ampicillin, a broad spectrum antibiotic and cloxacillin, a semi-synthetic beta-lactamase resistant

penicillin with activity against gram-negative and gram-positive bacteria including beta-lactamase producing staphylococci.

Both ampicillin and cloxacillin are bactericidal antibiotics and act by interfering with the formation of new bacterial cell wall by dividing organisms.

Mechanism of resistance

The main mechanism of resistance to ampicillin/cloxacillin is alteration of penicillin-binding proteins (PBPs), which reduce the affinity of the antibacterial agent for the target.

Breakpoints

Ampicillin sodium and cloxacillin sodium for injection breakpoints EUCAST Interpretive Criteria

	Ampicillin MIC breakpoint (mg/L)		Ampicillin Zone diameter breakpoint (mm) (2 µg disk)		Cloxacillin MIC breakpoint (mg/L)		Cloxacillin Zone diameter breakpoint (mm)		Cefoxitin Zone Diameter breakpoint (mm) (30 µg disk)	
	S ≤	R >	S ≥	R <	S ≤	R >	S ≥	R <		
Enterobacteriaceae	8	8	14	14	-	-	-	-	-	-
Staphylococcus saprophyticus	Note 1	Note 1	18	18	NOT e ¹	Note 1	NOT e ¹	Note 1	22	22
Staphylococcus aureus, Staphylococcus lugdunensis	-	-	-	-	-	-	-	-	22	22
Coagulate-negative Staphylococci other than S. saprophyticus and S. lugdunensis	-	-	-	-	-	-	-	-	25	25

¹ Most staphylococci are penicillinase producers, which are resistant to benzylpenicillin, phenoxymethylpenicillin, ampicillin, amoxicillin, piperacillin and ticarcillin. Isolates negative for penicillinase and susceptible to methicillin can be reported susceptible to these agents. Isolates positive for penicillinase and methicillin susceptible are susceptible to

beta-lactamase inhibitor combinations and isoxazolympenicillins(oxacillin,cloxacillin,dicloxacillinand flucloxacillin).Methicillin resistant isolates are, with few exceptions, resistant to all beta-lactamagents

5.2 Pharmacokinetic properties

The prevalence of acquired resistance is geographically and time dependent and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections.

The cloxacillin component of ampicillin sodium and cloxacillin sodium for injection covers exclusively the suspected or demonstrated presence of *Staphylococcus aureus*. Methicillin-susceptible *Staphylococcus aureus* (MSSA) and methicillin susceptible coagulase-negative staphylococcus (MSCoNS) are commonly susceptible to cloxacillin. MRSA and MRCoNS are resistant to cloxacillin. For all other indicated bacterial species, the susceptibility of ampicillin/cloxacillin is similar to ampicillin including limited activity against Gram-negative organisms.

<u>In vitro susceptibility of micro-organisms to Ampicillin</u>
<u>Commonly susceptible species</u>
Gram-positive aerobes: <i>Bacillus anthracis</i> Beta-hemolytic streptococci <i>Enterococcus faecalis</i> <i>Listeria monocytogenes</i> Gram-negative aerobes: <i>Bordetella pertussis</i>
<u>Species for which acquired resistance may be a problem</u>
Gram-negative aerobes: <i>Escherichia coli</i> <i>Haemophilus influenzae</i> <i>Salmonella</i> spp. <i>Shigella</i> spp. <i>Neisseria gonorrhoeae</i> <i>Pasteurella</i> spp. <i>Proteus mirabilis</i> <i>Vibrio cholera</i>
Gram-positive aerobes: <i>Corynebacterium</i> spp. <i>Staphylococcus</i> spp. including <i>Staphylococcus aureus</i> <i>Streptococcus pneumoniae</i> Viridans group streptococcus
Gram-positive anaerobes: <i>Clostridium</i> spp.
Gram-negative anaerobes: <i>Prevotella</i> spp.
<u>Inherently resistant organisms</u>
Gram-negative aerobes: <i>Acinetobacter baumannii</i> <i>Burkholderia cepacia</i> <i>Citrobacter freundii</i> <i>Citrobacter koseri</i> <i>Enterobacter aerogenes</i> <i>Enterobacter cloacae</i> <i>Escherichia hermannii</i> <i>Hafnia alvei</i> <i>Klebsiella pneumoniae</i>

<i>Morganellamorganii</i> <i>Proteus penneri</i> <i>Proteus vulgaris</i> <i>Providenciarettgeri</i> <i>Providenciastuartii</i> <i>Pseudomonas aeruginosa</i> <i>Serratiamarcescens</i> <i>Stenotrophomonasmaltophilia</i> <i>Yersinia enterocolitica</i>
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Pharmacokinetic Properties

Ampicillin has a plasma half-life of approximately 1-2 hours and is excreted mainly in the bile and urine.

Cloxacillin is excreted in the urine and bile with a serum half-life of approximately 30 minutes.

5.3 Preclinical safety data

Not applicable

6. Pharmaceutical particulars

6.1. List of Excipients

None.

6.2. Incompatibilities

Ampicillin sodium and cloxacillin sodium for injection should not be mixed with blood products or other proteinaceous fluids (e.g. protein hydrolysates) or with intravenous lipid emulsions.

If Ampicillin sodium and cloxacillin sodium for injection is prescribed concurrently with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because loss of activity of the aminoglycoside and possibly precipitation can occur under these conditions.

6.3. Shelf life

Powder in vials, 36 months.

6.4. Special precautions for storage

Store below 30°C away from light and humidity

6.5. Nature and contents of container

Clear glass vial, butyl stopper, flip-off cap

6.6. Special precautions for disposal and other handling

Ampicillin sodium and cloxacillin sodium for injection 500 mg may be added to most intravenous fluids (e.g. Water for Injections, sodium chloride 0.9%, glucose 5%, sodium chloride 0.18% with glucose 4%). In intravenous solutions containing glucose or other carbohydrates, Ampicillin sodium and cloxacillin sodium should be infused within one hour of preparation. Intravenous solutions of Ampicillin sodium and cloxacillin sodium in Water for Injections or sodium chloride 0.9% should be infused within 24 hours of preparation. Full particulars are given in the Package Enclosure Leaflet. Preparation of Ampicillin sodium and cloxacillin sodium infusion solutions must be carried out under appropriate aseptic conditions if these extended storage periods are required.

7. Marketing authorisation holder

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8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 11Dec 2020

10. Date of revision of the text

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