To be sold by retail on prescription of R.M.P. only

AMPOXIN CAPSULES

1. **Generic Name**

Ampicillin and Cloxacillin Capsules

2. Qualitative and quantitative composition

AMPOXIN 250

Each capsule contains:

Ampicillin Trihydrate I.P. equivalent to Ampicillin…..125 mg

Cloxacillin Sodium I.P. equivalent to Cloxacillin……..125 mg

Approved colours used in the capsule shell.

The excipients used are Talc, Colloidal Silicon Dioxide, Magnesium Stearate and HGC Size 2 Shells.

AMPOXIN 500

Each capsule contains:

Ampicillin Trihydrate I.P. equivalent to Ampicillin…..250 mg

Cloxacillin Sodium I.P. equivalent to Cloxacillin……..250 mg

Approved colours used in the capsule shell.

The excipients used are Talc, Colloidal Silicon Dioxide, Magnesium Stearate and HGC Size 0 Shells.

3. Dosage form and strength

Dosage form – Capsules

Strength –

Ampicillin Trihydrate I.P. equivalent to Ampicillin….125/250mg

Cloxacillin Sodium I.P. equivalent to Cloxacillin…….125/250 mg

4. Clinical particulars

4.1 Therapeutic indication

AMPOXIN is indicated for the treatment of the following infections including mixed Gram-positive (except methicillin-resistant Staphylococcus aureus (MRSA) and methicillin-resistant coagulase-negative staphylococcus (MRCoNS)) and Gram-negative infections:

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

Respiratory infections: bronchopneumonia, acute exacerbations of chronic bronchitis.

***Obstetrics*:** puerperal fever.

Other infections such as septicaemia, bone infections e.g., osteomyelitis, ear, nose and throat infections.

Appropriate culture and susceptibility tests should be performed before treatment in order to isolate and identify organisms causing infection and to determine their susceptibility to

AMPOXIN. Where treatment is initiated before results are available expert advice should be sought when the local prevalence of resistance is such that the utility of AMPOXIN is questionable (see Pharmacological properties, Pharmacodynamics).

4.2 Posology and method of administration

Dose: As directed by the Physician

Route	**Dosage**
Adults and Elderly	
Oral	**1 to 2g every 6 hours**
Children **2 to 12 years**	
Oral	Half adult dose

The dose of AMPOXIN may be increased for the treatment of severe infections.

Renal **impairment**

In cases of renal failure, the dosage should be adapted as per guidance of physician.

Hepatic **impairment**

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

Mode of Administration

Oral route**:**

AMPOXIN should be administered 0.5 to 1 hour before meals.

4.3 Contraindications

Ampicillin and cloxacillin

AMPOXIN should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g., penicillins, cephalosporins) or excipients (See List of Excipients). – AMPOXIN is contraindicated for ocular administration.

4.4 Special warnings and precautions for use

Caution should be observed when administering AMPOXIN to babies whose mothers are hypersensitive to penicillin.

Before initiating therapy with AMPOXIN, careful inquiry should be made concerning previous hypersensitivity reactions to beta-lactams.

Cross-sensitivity between penicillins and cephalosporins is well documented.

Serious and occasionally fatal hypersensitivity reactions (anaphylaxis) have been reported in patients receiving beta-lactam antibiotics. Although anaphylaxis is more frequent following Parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more like to occur in individuals with a history of beta-lactam hypersensitivity.

If an allergic reaction occurs, AMPOXIN should be discontinued and the appropriate alternative therapy instituted. All adverse reactions should be treated symptomatically. AMPOXIN should be avoided if infectious mononucleosis and/or acute or chronic leukaemia

of lymphoid origin are suspected. The occurrence of a skin rash has been associated with these Conditions following the administration of ampicillin.

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

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 Dosage and Administration,

Renal impairment).

Cloxacillin can displace bilirubin from protein-binding sites. Normal caution should therefore be exercised in the treatment of jaundiced neonates.

4.5 Drugs interactions

- Bacteriostatic drugs may interfere with the bactericidal action of ampicillin.

- Probenecid decreases the renal tubular secretion of ampicillin. Concurrent use with ampicillin may result in increased and prolonged blood levels of ampicillin.
- Concurrent administration of allopurinol during treatment with ampicillin can increase the likelihood of allergic skin reactions.
- It is recommended that when testing for the presence of glucose in urine during ampicillin treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of ampicillin, false positive readings are common with chemical methods.
- In common with other antibiotics, AMPOXIN may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.
- Sulphonamides and acetylsalicylic acid inhibit serum protein binding of cloxacillin in vitro. This may result in increased levels of free cloxacillin in serum in vivo.

4.6 Use in special populations (such as pregnant women, lactating women, paediatric patients, geriatric patients etc.)

Pregnancy:

Adequate human data on use during pregnancy are not available. However, animal studies have not identified any risk to pregnancy or embryo-foetal development. **Lactation:**

Adequate human and animal data on use during lactation are not available. **4.7 Effects on ability to drive and use machines**

No adverse effects on the ability to drive or operate machinery have been observed.

4.8 Undesirable effects

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 reported clinical trial 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

Rare: Prolongation of bleeding time and prothrombin time

Very rare: Hemolytic anemia, leucopenia, thrombocytopenia, and agranulocytosis

Immune system disorders

Very rare: Anaphylaxis (See Warnings and Precautions) and other hypersensitivity 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 Warnings and Precautions) and haemorrhagic colitis

Hepatobiliary 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).

Not Known: Acute Generalised Exanthematous Pustulosis (AGEP)

Renal and urinary disorders

Very rare: Interstitial nephritis

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

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine

4.9 Overdose

Overdosage with oral AMPOXIN 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. These symptoms should be treated symptomatically.

5. Pharmacological properties

5.1 Mechanism of Action

Ampicillin

Ampicillin is in the penicillin group of beta-lactam antibiotics and is part of the amino penicillin family. It is roughly equivalent to amoxicillin in terms of activity. Ampicillin is able to penetrate Gram-positive and some Gram-negative bacteria. It differs from penicillin G, or Benzylpenicillin, only by the presence of an amino group. This amino group, present on both ampicillin and amoxicillin, helps these antibiotics pass through the pores of the outer membrane of Gram-negative bacteria, such as *E. coli*, *Proteus mirabilis*, *Salmonella enterica*, and *Shigella*.

Ampicillin acts as an irreversible inhibitor of the enzyme transpeptidase, which is needed by bacteria to make the cell wall.[2] It inhibits the third and final stage of bacterial cell wall synthesis in binary fission, which ultimately leads to cell lysis; therefore, ampicillin is usually bacteriolytic

Cloxacillin

Cloxacillin exerts a bacterial action against susceptible microorganisms during the stage of active multiplication. It acts through the inhibition of biosynthesis of cell wall mucopeptides. Cloxacillin demonstrates activity against strains of beta-hemolytic streptococci, pneumococci, penicillin G sensitive staphylococci and, due to its resistance to penicillinase, penicillin G resistant (β-lactamase producing) staphylococci. Cloxacillin displays less intrinsic antibacterial activity and a narrower spectrum than penicillin G.

5.2 Pharmacodynamic properties

AMPOXIN is a combination of ampicillin and cloxacillin. Cloxacillin is a narrow-spectrum antibiotic of the isoxazolyl penicillin group; it is not inactivated by staphylococcal beta lactamases. Ampicillin is a broad-spectrum antibiotic of the amino penicillin group; it is not resistant to beta-lactamases.

Both ampicillin and cloxacillin are bactericidal antibiotics and act by interfering with the formation of new bacterial cell wall by dividing organisms. The prevalence of acquired resistance is geographically variable and for select species may be very high. Local information on resistance is desirable, particularly when treating severe infections. AMPOXIN susceptibility rates are higher than ampicillin rates due to the cloxacillin activity against β-lactamase producing staphylococci. Methicillin-susceptible Staphylococcus aureus (MSSA) and methicillin-susceptible coagulase-negative staphylococcus (MSCoNS) are commonly susceptible to AMPOXIN. MRSA and MRCoNS are resistant to AMPOXIN. For all other indicated bacterial species, the susceptibility of AMPOXIN is similar to ampicillin including limited activity against Gram-negative organisms.

5.3 Pharmacokinetic properties

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

Both ampicillin and cloxacillin are stable in the gastric environment resulting in good absorption. Neither component of the combination of ampicillin and cloxacillin interferes with the absorption or excretion of the other. The total quantity absorbed by the oral route represents 50% (cloxacillin) and 40% (ampicillin) of the quantity administered. 8 The presence of food in the stomach may depress oral absorption and AMPOXIN should therefore be taken 0.5 to 1 hour before meals.

Distribution

AMPOXIN diffuses well into most tissues and body fluids including, among others, bronchial secretions, sinuses, saliva, cerebrospinal fluid (variable percentage depending on the degree of meningeal inflammation), bile, serous membranes and middle ear. Crossing the meningeal barrier: AMPOXIN diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed. Crossing into breast milk: AMPOXIN is excreted in small quantities in breast milk. Plasma half-life for cloxacillin is 0.5 to 1 hour and 1 to 1.5 hour for ampicillin. Protein binding: the serum protein binding proportion is approximately 94% for cloxacillin and 18% for ampicillin. Metabolism in normal subjects approximately 20% (cloxacillin) and 40% (ampicillin) of the dose administered is metabolised.

Excretion

AMPOXIN is eliminated mainly through the kidney. Approximately 30% of the dose administered orally and over 60% of the ampicillin dose administered parenterally is eliminated in active form in the urine within 24 hours. The equivalent percentages for cloxacillin are approximately 20% and 30% respectively. A small proportion (10%) of the dose administered is excreted in bile.

6. Nonclinical properties

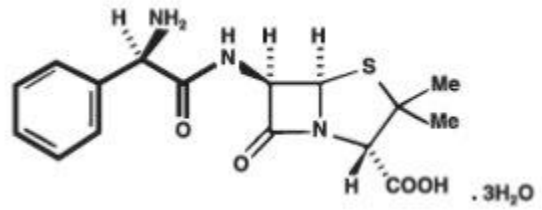
6.1 Animal Toxicology or Pharmacology

No further information of relevance to add.

7. Description

<u>Ampicillin Trihydrate</u>

Ampicillin Trihydrate is a semisynthetic penicillin derived from the basic penicillin nucleus, 6-aminopenicillanic acid. Ampicillin is designated chemically as (6R)-6-(α-phenyl-D-glycyl-amino) penicillanic acid trihydrate. It has the following chemical structure:



The molecular formula is $C_{16}H_{19}N_3O_4S.3H_2O$, and the molecular weight is 403.5. Ampicillin trihydrate is white, crystalline powder which is slightly soluble in water; soluble in dilute solution of acids and of alkali hydroxides; practically insoluble in ethanol, in chloroform, in ether and in fixed oils.

<u>Cloxacillin Sodium</u>

Cloxacillin Sodium is sodium (6R)-6-[3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamido] penicillanate monohydrate. The molecular formula is $C_{19}H_{17}ClN_3NaO_5S.H_2O$, and the molecular weight is 475.9. Cloxacillin Sodium is white or almost white, crystalline powder, hygroscopic which is freely soluble in water and in methanol; soluble in ethanol; slightly soluble in chloroform.

AMPOXIN 250

Ampicillin and Cloxacillin Capsules are Size "2" hard gelatin capsule with transparent purple body and opaque blue cap, "Ampoxin 250 mg" printed in blue on body in circular printing and "Torrent logo" (3RPT) printed in white on cap in circular printing containing white powder with a creamish hue. The excipients used are Talc, Colloidal Silicon Dioxide, Magnesium Stearate and HGC Size 2 Shells.

AMPOXIN 500

Ampicillin and Cloxacillin Capsules are Size "0" hard gelatin capsule with transparent purple body and opaque brown cap, "Ampoxin 500 mg" printed in blue on body in circular printing and "Torrent logo" (3RPT) printed in white on cap in circular printing containing white powder with a creamish hue. The excipients used are Talc, Colloidal Silicon Dioxide, Magnesium Stearate and HGC Size 0 Shells.

8. Pharmaceutical particulars

8.1 Incompatibilities

AMPOXIN must not be dissolved in either protein or protein hydrolysate solutions or in lipid solutions, or in blood or plasma. When AMPOXIN is prescribed together with an aminoglycoside, the two antibiotics should not be mixed in the same container as the one containing the infusion solution because a loss of activity may occur.

8.2 Shelf-life

Do not use later than the date of expiry.

8.3 Packaging information

AMPOXIN is available in Strip pack of 15 capsules

8.4 Storage and handing instructions

Store in a cool and dry place. Protect from light and moisture.

9. Patient Counselling Information

Patient Counselling Information

Package leaflet: Information for the patient AMPOXIN

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects talk to your doctor or pharmacist.

This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet?

9.1.What AMPOXIN is and what it is used for

9.2.What you need to know before you take AMPOXIN

9.3.How to take AMPOXIN

9.4.Possible side effects

9.5.How to store AMPOXIN

9.6.Contents of the pack and other information

9.1 **What AMPOXIN is and what it is used for**

AMPOXIN is an antibiotic and works by killing bacteria that cause infections. It contains two different medicines called ampicillin and cloxacillin. They both belong to a group of antibiotics called 'penicillins'

AMPOXIN is combination of Ampicillin (has a broad spectrum of bactericidal activity against many gram-positive and gram-negative aerobic and anaerobic bacteria. It acts through the inhibition of cell wall mucopeptide biosynthesis during the stage of active multiplication.)

Cloxacillin (Cloxacillin prevents bacteria from reproducing, which allows your body to fight only the existing bacteria)

AMPOXIN **is indicated for**

- Infected wounds or lung infections following surgery
- Respiratory tract infections
- Fever associated with bacterial infection.

9.2 What you need to know before you take AMPOXIN

WARNINGS AND PRECAUTIONS

BEFORE you use AMPOXIN talk to your doctor or pharmacist if you have:

Do not have AMPOXIN if you:

- Are allergic (hypersensitive) to amoxicillin, cloxacillin or penicillin
- Have ever had an allergic (hypersensitive) reaction to any antibiotic. This can include a skin rash or swelling of the face or neck. Do not have AMPOXIN if any of the above apply. If you are not sure, talk to your doctor, pharmacist or nurse before having AMPOXIN**.**
- Take special care with AMPOXIN Check with your doctor, pharmacist or nurse before having this medicine if you:
- Have ever had any reactions to antibiotics, including a skin rash or swelling of the face or neck when taking any antibiotic
- Are being treated for kidney or liver problems
- Have glandular fever and/or leukaemia as you may develop a rash if you have these conditions and take ampicillin
- Are on a diet that restricts the amount of sodium you can eat. If this medicine is being given to your baby, tell your doctor:
- If you (mother) are allergic to penicillin
- If your baby has jaundice (yellowing of the skin and/or eyes). If you are not sure if any of the above apply to you, talk to your doctor, pharmacist or nurse before you AMPOXIN.

Other medicines and AMPOXIN

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Look out for important symptoms

AMPOXIN can make some existing conditions worse, or cause serious side effects such as allergic reactions and severe diarrhoea. You must look out for certain symptoms while you are taking AMPOXIN, to help reduce the risk of any problems.

- If you are taking probenecid (used for gout), your doctor may decide to adjust your dose of AMPOXIN.
- If you are taking allopurinol (used for gout) with AMPOXIN, it may be more likely that you'll have an allergic skin reaction.
- If you are taking Sulphonamides and acetylsalicylic acid, your doctor may decide to adjust your dose of AMPOXIN.
- AMPOXIN may stop the contraceptive pill working. You will need to use extra contraceptive precautions, such as using a condom. If you need any advice, talk to your doctor, pharmacist or nurse.

Pregnancy and breast-feeding

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine

9.3 How to take AMPOXIN

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

- If you are taking this medicine for a long time, your doctor will want to monitor you (particularly if you are taking it for more than a year).
- If your doctor has told you to take this medicine as and when you need it, tell your doctor if your symptoms change.

How much to take

Your doctor will tell you how many tablets to take and how long to take them for. This will depend on your condition, how old you are and how well your liver works.

9.4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you notice any of the following serious side effects, stop taking AMPOXIN and contact a doctor immediately:

Tell your doctor or nurse straight away if you notice any of the following serious side effects – you may need urgent medical treatment:

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 reported clinical trial 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: An excessive breakdown of red blood cells causing a form of anaemia. Signs include: tiredness, headaches, shortness of breath, dizziness, looking pale and yellowing of the skin and the whites of the eyes, leucopenia ("deficit in the number of white blood cells")., thrombocytopenia (blood does not have enough platelets. Platelets are circulating cell fragments that help with blood clotting, so having too few of them in your blood can lead to problems controlling bleeding.).

Immune system disorders:

Allergic reactions, the signs may include: skin itching or rash, swelling of the face, lips, tongue, body or breathing difficulties.

Rash or pinpoint flat red round spots under the skin surface or bruising of the skin. This is due to inflammation of blood vessel walls due to an allergic reaction. It can be associated with joint pain (arthritis) and kidney problems. If any hypersensitivity reaction occurs, the treatment should be discontinued.

Nervous system disorders

Very rare:

fits (convulsions), seen in patients on high doses or with kidney problems

Sudden, involuntary jerking or a muscle or group of muscles

Gastrointestinal disorders

Common: feeling sick (nausea), diarrhoea.

Uncommon: Vomiting

Rare: Inflammation of the large bowel (colon) with diarrhoea sometimes containing blood, pain and fever

Hepatobiliary disorders

Very rare: serious liver side effects may occur which are often reversible. You must tell your doctor or nurse urgently if you get: - severe diarrhoea with bleeding - blisters, redness or bruising of the skin - darker urine or paler stools - yellowing of the skin or the whites of the eyes (jaundice). See also anaemia below which might result in jaundice. These can happen when having the medicine or for up

Skin and subcutaneous tissue disorders

Common: a skin reaction known as 'erythema multiforme' where you may develop: itchy reddish purple patches on the skin especially on the palms of the hands or soles of the feet, 'hive-like' raised swollen areas on the skin, tender areas on the surfaces of the mouth, eyes and private parts. You may have a fever and be very tired

Other severe skin reactions can include: changes in skin colour, bumps under the skin, blistering, pustules, peeling, redness, pain, itching, scaling. These may be associated with fever, headaches and body aches

High temperature (fever), chills, a sore throat or other signs of an infection, or if you bruise easily. These may be signs of a problem with your blood cells

Renal and urinary disorders

Very rare: kidney problems

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at:

http://www.torrentpharma.com/Index.php/site/info/adverse_event_reporting.

By reporting side effects, you can help provide more information on the safety of this medicine

9.5 How to store AMPOXIN

Store in a cool and dry place. Protect from light and moisture.

9.6 Contents of the pack and other information

What AMPOXIN contains

The active substances AMPOXIN are Ampicillin and Cloxacillin.

AMPOXIN 250

The excipients used are Talc, Colloidal Silicon Dioxide, Magnesium Stearate and HGC Size 2 Shells.

AMPOXIN 500

The excipients used are Talc, Colloidal Silicon Dioxide, Magnesium Stearate and HGC Size 0 Shells.

10. Details of manufacturer

a. Manufactured by:

Torrent Pharmaceuticals Ltd.

Indrad – 382721, Dist. Mehsana, INDIA

At: Plot No. 21, 22, Pharmacity, Selaqui, Dehradun, and Uttarakhand.

b. Manufactured by:

Torrent Pharmaceuticals Ltd.

Indrad – 382721, Dist. Mehsana, INDIA

At: Plot No. 16, Vardhman Industrial Estate, Vill – Bahadarpur Saini,

N.H. 58, Haridwar – 247667, Uttarakhand.

11. Details of permission or licence number with date

a. Mfg Lic.No. 92/UA/LL/SC/P-2017 issued on 04.01.2018

b. Mfg Lic.No. 24/UA/LL/SC/P/2015 issued on 01.01.2018

12. Date of revision

Not Applicable

MARKETED BY