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

AMPOXIN DRY SYRUP

1. Generic Name

Ampicillin and Cloxacillin for Oral Suspension

2. Qualitative and quantitative composition

After reconstitution, each 5ml contains:

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

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

Colour: Erythrosine

The excipients used are Colloidal Silicon Dioxide, Ethyl Cellulose, Sodium Carboxymethylcellulose, Sodium Benzoate, Disodium Edetate, Sodium Chloride, Aspartame, Erythrosine Supra Colour, Trushil Peppermint Special Flavour, Sucrose and Methylene Chloride.

3. Dosage Form and Strength

Dosage Form: Syrup

Strength: Ampicillin 125 mg, Cloxacillin 125 mg

4. Clinical particulars

4.1 Therapeutic indication

Ampoxin Dry Syrup 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.

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 Dry Syrup.

4.2 Posology and method of administration

Dose: As directed by the physician

Mode of Administration

Oral route:

Direction for use

Add boiled and cooled water up to the ring on the bottle and shake vigorously. Adjust the volume up to the ring by adding more water if necessary. This makes 30ml of suspension.

Consume within 3 days after reconstitution. Store the reconstituted suspension below 25°C.

The dose of Ampoxin dry syrup 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**

In cases of hepatic impairment, the dosage and frequency should be adapted as per guidance of physician.

Mode of Administration

***Oral route*:**

Ampoxin Dry Syrup should be administered 0.5 to 1 hour before meals.

4.3 Contraindications

Ampicillin and cloxacillin

Ampoxin Dry Syrup should not be given to patients with a history of hypersensitivity to beta-lactam antibiotics (e.g., penicillins, cephalosporins) or excipients

Ampoxin Dry Syrup is contraindicated for ocular administration.

4.4 Special warnings and precautions for use

Before initiating therapy with Ampoxin Dry Syrup, 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 likely to occur in individuals with a history of beta-lactam hypersensitivity.

If an allergic reaction occurs, Ampoxin Dry Syrup should be discontinued and the appropriate alternative therapy instituted. All adverse reactions should be treated symptomatically.

Ampoxin Dry Syrup 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.

Ampoxin Dry Syrup contain sodium benzoate which is a mild irritant to the skin, eyes, and mucous membrane. It may increase the risk of jaundice in newborn babies.

4.5 Drugs interactions

Probenecid decreases the renal tubular excretion of Ampoxin Dry Syrup. Concurrent use with Ampoxin Dry Syrup may result in increased and prolonged blood levels of Ampoxin Dry Syrup**.**

In common with other antibiotics, Ampoxin Dry Syrup 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*.

Bacteriostatic drugs may interfere with the bactericidal action of Ampoxin Dry Syrup.

Concurrent administration of allopurinol during treatment with Ampoxin Dry Syrup can increase the likelihood of allergic skin reactions.

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

Pregnancy and Lactation

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

The following statements reflect the information available on the adverse reaction profile of the individual constituents (ampicillin and cloxacillin) and/or the combination in Ampoxin Dry Syrup. The majority of the adverse reactions listed below are not unique to ampicillin - cloxacillin 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 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: 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).

4.9 Overdose

Overdosage with oral Ampoxin Dry Syrup 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 benzyl penicillin 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 Benzyl penicillin, 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 Trans peptidase, 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 mucopeptide. 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 Dry Syrup 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 Dry Syrup 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 Dry Syrup. MRSA and MRCoNS are resistant to Ampoxin Dry Syrup. For all other indicated bacterial species, the susceptibility of Ampoxin Dry Syrup is similar to ampicillin including limited activity against Gram-negative organisms.

5.3 Pharmacokinetic properties

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. The presence of food in the stomach may depress oral absorption, so Ampoxin Dry Syrup should therefore be taken 0.5 to 1 hour before meals.

Distribution

Ampoxin Dry Syrup 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 Dry Syrup diffuses in only small proportion into the cerebrospinal fluid of subjects whose meninges are not inflamed. Crossing into breast milk: Ampoxin Dry Syrup 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 Dry Syrup 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

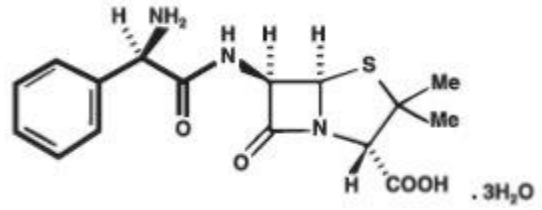
6.1 Animal Toxicology or Pharmacology

Reproduction studies have been performed in laboratory animals at doses several times the human dose and have revealed no evidence of adverse effects due to ampicillin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

7. Description

Ampicillin Trihydrate

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.

Cloxacillin Sodium

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.

Ampicillin and Cloxacillin for Oral Suspension is colourless to slight pink free flowing powder, which on reconstitution gives pink, coloured suspension. The excipients used are Colloidal Silicon Dioxide, Ethyl Cellulose, Sodium Carboxymethylcellulose, Sodium Benzoate, Disodium Edetate, Sodium Chloride, Aspartame, Erythrosine Supra Colour, Trushil Peppermint Special Flavour, Sucrose and Methylene Chloride.

8. Pharmaceutical particulars

8.1 Incompatibilities

Ampoxin Dry Syrup must not be dissolved in either protein or protein hydrolysate solutions or in lipid solutions, or in blood or plasma. When Ampoxin Dry Syrup 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 Dry Syrup is available in amber glass bottle of 30ml.

8.4 Storage and handing instructions

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

Store the reconstituted suspension below 25°C.

Shake well before use.

9. Patient Counselling Information

Package leaflet: Information for the patient Ampoxin Dry Syrup

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 Dry Syrup is and what it is used for

9.2.What you need to know before you take Ampoxin Dry Syrup

9.3.How to take Ampoxin Dry Syrup

9.4.Possible side effects

9.5.How to store Ampoxin Dry Syrup

9.6.Contents of the pack and other information

9.1 **What Ampoxin Dry Syrup is and what it is used for**

Ampoxin Dry Syrup 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'

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 Dry Syrup 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 Dry Syrup

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 Dry Syrup if any of the above apply. If you are not sure, talk to your doctor, pharmacist or nurse before having Ampoxin Dry Syrup**.**

Take special care with Ampoxin Dry Syrup

- 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 have Ampoxin..

Other medicines and Ampoxin Dry Syrup

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

Look out for important symptoms

Ampoxin Dry Syrup 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 Dry Syrup.

- If you are taking allopurinol (used for gout) with Ampoxin Dry Syrup, 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 Dry Syrup.

Ampoxin Dry Syrup 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 Dry Syrup

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 Dry Syrup 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 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 Dry Syrup

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

Store the reconstituted suspension below 25°C

9.6 Contents of the pack and other information

What Ampoxin Dry Syrup contains

•The active substance is Ampicillin Trihydrate and Cloxacillin Sodium

•The other ingredients are Colloidal Silicon Dioxide, Ethyl Cellulose, Sodium Carboxymethylcellulose, Sodium Benzoate, Disodium Edetate, Sodium Chloride, Aspartame, Erythrosine Supra Colour, Trushil Peppermint Special Flavour, Sucrose and Methylene Chloride.

Ampoxin Dry Syrup is available in amber glass bottle of 30ml.

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

TORRENT PHARMACEUTICALS LTD.

IN/ AMPOXIN DRY SYRUP 125 mg, 125 mg /APR-20/01/PI