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

AMPOXIN

1. Generic Name

Ampicillin and Cloxacillin for Injection

2. Qualitative and quantitative composition

AMPOXIN 250

Each vial contains:

Ampicillin Sodium I.P. equivalent to Anhydrous Ampicillin……125 mg

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

AMPOXIN 500

Each vial contains:

Ampicillin Sodium I.P. equivalent to Anhydrous Ampicillin……250 mg

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

AMPOXIN 1g

Each vial contains:

Ampicillin Sodium I.P. equivalent to Anhydrous Ampicillin……500 mg

Cloxacillin Sodium I.P. equivalent to Cloxacillin ……....500 mg

3. Dosage form and strength

Dosage form – Injection

Strength

Ampicillin Sodium I.P. equivalent to Anhydrous Ampicillin….125/250/500 mg

Cloxacillin Sodium I.P. equivalent to Cloxacillin……...125/250/500 mg

4. Clinical particulars

4.1 Therapeutic indication

Ampoxin is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the following conditions:

Respiratory Tract Infections caused by S. pneumoniae, Staphylococcus aureus (penicillinase and non penicillinase-producing), and H. influenzae and Group A beta-hemolytic Streptococci.

Bacterial Meningitis caused by E. coli, Group B Streptococci, and other Gram-negative bacteria (Listeria monocytogenes, N. meningitidis). The addition of an aminoglycoside with ampicillin may increase its effectiveness against Gram-negative bacteria.

Septicemia and Endocarditis caused by susceptible Gram-positive organisms including Streptococcus spp., penicillin G-susceptible staphylococci and enterococci. Gram-negative sepsis caused by E. coli, Proteus mirabilis and Salmonella spp. responds to ampicillin. Endocarditis due to enterococcal strains usually respond to intravenous therapy. The addition of an aminoglycoside may enhance the effectiveness of ampicillin when treating streptococcal

Endocarditis.

Urinary Tract Infections caused by sensitive strains of E. coli and Proteus mirabilis.

Gastrointestinal Infections caused by Salmonella typhi (typhoid fever), other Salmonella spp. and Shigella spp. (dysentery) usually respond to oral or intravenous therapy. Bacteriology studies to determine the causative organisms and their susceptibility to ampicillin should be performed. Therapy may be instituted prior to obtaining results of susceptibility testing.

It is advisable to reserve the parenteral form of this drug for moderately severe and severe infections and for patients who are unable to take the oral forms. A change to oral ampicillin may be made as soon as appropriate. Indicated surgical procedures should be performed. To reduce the development of drug-resistant bacteria and maintain the effectiveness of Ampicillin for Injection, USP and other antibacterial drugs, Ampicillin for Injection, USP should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

4.2 Posology and method of administration

AMPOXIN 250 - Direction for use: Dissolve the contents of the vial in 2 ml of sterile water for injection IP to make final volume of 2.15 ml for IM use or in 5 ml to make final volume of 5.15 ml for IV use.

AMPOXIN 500 - Direction for use: Dissolve the contents of the vial in 3 ml of sterile water for injection IP to make final volume of 3.3 ml for IM use or in 5 ml to make final volume of 5.3 ml for IV use.

AMPOXIN 1g - Direction for use: Dissolve the contents of the vial in 3 ml of sterile water for injection IP to make final volume of 3.7 ml for IM use or in 5 ml to make final volume of 5.7 ml for IV use.

The reconstituted solution should be used immediately after preparation.

4.3 Contraindications

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

AMPOXIN is contraindicated for ocular administration.

4.4 Special warnings and precautions for use

Ampicillin

WARNINGS

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more apt to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens.

There have been well-documented reports of individuals with a history of penicillin hypersensitivity reactions who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Before initiating therapy with a penicillin, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens. If an allergic reaction occurs, the drug should be discontinued and appropriate

therapy instituted.

SERIOUS ANAPHYLACTOID REACTIONS REQUIRE IMMEDIATE EMERGENCY TREATMENT WITH EPINEPHRINE, OXYGEN, INTRAVENOUS STEROIDS, AND AIRWAY MANAGEMENT, INCLUDING INTUBATION, SHOULD ALSO BE ADMINISTERED AS INDICATED.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including Ampicillin for Injection, USP, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibacterial drug use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibacterial drug use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibacterial treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PREACATIONS

General: A high percentage of patients with infectious mononucleosis or lymphatic leukemia who receive ampicillin develop a skin rash, and the drug should not be administered to such patients. In most cases, the rash is maculopapular, pruritic, and generalized. Prolonged use of antibiotics may promote overgrowth of no susceptible organisms. Superinfections occur, appropriate measures should be taken

Before therapy, inquiry as to past penicillin or other allergies is essential as reactions occur more frequently in hypersensitive persons. During therapy, if allergic or anaphylactic reactions occur, discontinue treatment and initiate usual measures, i.e. antihistamines, pressor amines or corticosteroids. During long-term therapy, renal, hepatic, and hematopoietic functions should be checked periodically. Candidiasis and other superinfections may occur, especially in debilitated and malnourished patients, or those with low resistance to infection due to corticosteroids, immunosuppresses or irradiation.

Cloxacillin

Hematologic:

During long-term therapy, renal, hepatic and hematopoietic functions should be checked periodically.

Hepatic:

During long-term therapy, renal, hepatic and hematopoietic functions should be checked periodically.

Immune:

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients receiving penicillin or cephalosporin therapy. These reactions are more apt to occur in individuals with a history or sensitivity to multiple allergens. Careful inquiry should be made concerning previous hypersensitivity to reactions to penicillins, cephalosporins or other

allergens. If allergic or anaphylactic reactions occurs, discontinue treatment and administer the usual agents, e.g. antihistamines, pressor amines, corticosteroids. See Contraindications.

Neurologic:

The passage of any penicillin from blood into brain is facilitated by inflamed meninges and during cardiopulmonary bypass. In the presence of such factors, particularly in renal failure when high serum concentration can be attained, CNS adverse effects including myoclonia, convulsive seizures and depressed consciousness can be expected. Although this complication has not been reported with cloxacillin, it should be anticipated.

Sensitivity/Resistance:

Candidiasis and other superinfections may occur, especially in debilitated and malnourished patients, or those with low resistance to infection due to corticosteroids, Immunosuppresors or irradiation. If superinfection occurs, institute appropriate measures.

Renal:

During long-term therapy, renal, hepatic and hematopoietic functions should be checked periodically.

Special Populations

Pregnant Women:

Safety in pregnancy has not yet been established.

Paediatrics:

Experience in premature and newborn infants is limited. Cautious administration of the drug to such patients and frequent evaluation of organ system function is recommended.

4.5 Drugs interactions

Ampicillin

Drug Interactions: The concurrent administration of allopurinol and ampicillin containing medicines increases substantially the incidence of rashes in patients receiving both drugs as compared to patients receiving ampicillin alone. It is not known whether this potentiation of ampicillin rashes is due to allopurinol or to hyperuricemia present in these patients. Ampicillin and aminoglycosides should not be reconstituted together due to the in vitro inactivation of the aminoglycosides by the Ampicillin.

Drug/Laboratory Test Interactions: Following administration of ampicillin to pregnant, women, a transient decrease in plasma concentration of total conjugated estriol, estriol Glucuronide, conjugated estrone and estradiol has been noted. With high urine concentrations of ampicillin, false-positive urinary glucose reactions may occur if copper reduction methods are used. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions be employed.

Probenecid

As with other penicillins, concurrent administration of probenecid enhances the serum concentration of cloxacillin.

Use in Elderly: There are no known specific precautions for the use of ampicillin in the elderly.

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

Pregnancy: Ampoxin has shown no teratogenic effects. 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.

Lactation: Ampicillin is excreted in trace amounts in human milk. Safety has not been established in lactating mothers. Therefore, caution should be exercised when ampicillin is administered to a nursing mother.

Use in Elderly: There are no known specific precautions for the use of the drug in the elderly.

Paediatrics: Experience in premature and newborn infants is limited. Cautious administration of the drug to such patients and frequent evaluation of organ system function is recommended.

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

Gastrointestinal Disturbances: Clostridium difficile associated diarrhea (CDAD)

Glossitis, stomatitis, black "hairy" tongue, nausea, vomiting, epigastric discomfort, flatulence and loose stools have been noted in some patients.

Hypersensitivity Reactions: Erythematous maculopapular rashes have been reported fairly frequently; uriticaria, erythema multiforme, and a few cases of exfoliative dermatitis have been observed. Anaphylaxis is the most serious reaction usually associated with parenteral administration.

Nervous system disorders

Myclonus and convulsions

Skin and subcutaneous tissue disorders

Acute Generalised Exanthematous Pustulosis (AGEP), Bullous reactions (including erythema multiforme, Stevens-Johnson syndrome and toxic epidermal necrolysis), exfoliative dermatitis and purpura

Uriticaria, other skin rashes, and serum sickness like reactions may be controlled with antihistamines, and if necessary, systemic corticosteroids. Serious anaphylactic reactions require the immediate use of epinephrine, oxygen and i.v. corticosteroids. In cases of infectious mononucleosis, where ampicillin has been administered, an extremely high incidence of generalized rash has been reported.

It may be expected the most common untoward reactions will be related to sensitivity. They are more likely to occur in individuals who have previously demonstrated hypersensitivity to penicillins and cephalosporins and in those with a history of allergy, asthma, hay fever or urticaria. All degrees of hypersensitivity, including fatal anaphylaxis, have been reported with penicillin.

Renal: Interstitial nephritis has been reported.

Ototoxicity: Ampicillin may be ototoxic when given i.v. in very high doses.

Hepatic: Hepatitis and cholestatic jaundice

A mild transitory elevation of serum glutamic oxaloacectic transaminase (SGOT) in individuals receiving large (2 to 4 times recommended dose) and often repeated i.m. injections. Evidence indicates that serum glutamic oxaloacetic transaminase (SGOT) is released at the site of i.m. injection of sodium ampicillin and that the presence of the enzyme in the blood does not necessarily indicate liver involvement.

Hematologic Disturbances:

Eosinophilia, leucopenia, anemia, thrombocytopenia, haemolytic anaemia, thrombocytopenic, purpura, neutropenia and agranulocytosis have been reported during therapy with penicillins. These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. Thrombophlebitis has occurred during the course of i.v. therapy. Mildly elevated SGOT level (less than 100 units) have been reported.

Immune:

Allergic reactions (rash, urticaria) including wheezing and sneezing have been reported.

4.9 Overdose

Treatment is likely needed only in patients with severely impaired renal function, since patients with normal kidneys excrete penicillins at a fast rate.

In case of overdosage, discontinue medication, treat symptomatically and institute supportive measures as required. In patients with renal function impairment, ampicillin class antibiotics can be removed by hemodialysis but not by peritoneal dialysis.

In patients with severe allergic reactions, general supportive measures (if the patient is in shock) or symptomatic therapy similar to that applied in all cases of hypersensitivity are recommended.

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. 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

Absorption

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 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

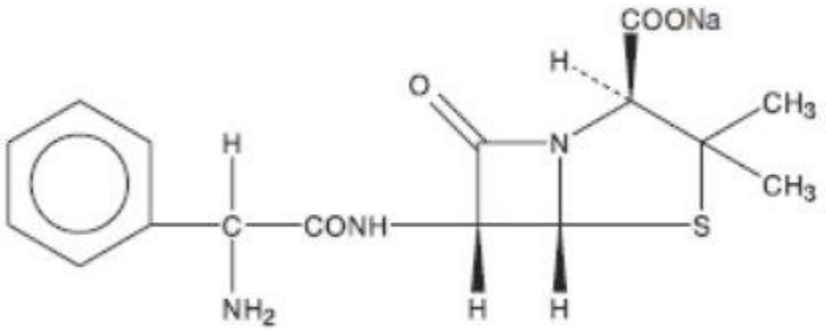
6.1 Animal Toxicology or Pharmacology

Animal studies have shown no teratogenic effects. 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. 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.

7. Description

Ampicillin Sodium

Ampicillin is the monosodium salt of [2S-[2α, 5α, 6β(S*)]]-6-[(aminophenylacetyl) amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid. It is an antibacterial agent with a broad spectrum of bactericidal activity against both penicillin-susceptible Gram-positive organisms and many common Gram-negative pathogens. Ampicillin is a white, crystalline powder. The molecular formula is $C_{16}H_{18}N_3NaO_4S$, and the molecular weight is 371.39. It has the following molecular structure:



Cloxacillin Sodium is sodium (6R)-6-[3-(2-chlorophenyl)-5-methylisoxazole-4-carboxamido] penicillanate monohydrate. The molecular formula is $C_{19}H_{17}ClN_3NaO_5S$, H2O 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 for Injection is White to almost white free flowing powder with creamish hue filled in 7.5 ml glass vial, plugged with grey butyl rubber stopper and sealed with red aluminum seal.

AMPOXIN 500

Ampicillin and Cloxacillin for Injection is White to almost white free flowing powder with creamish hue filled in 7.5 ml glass vial, plugged with grey butyl rubber stopper and sealed with red aluminum seal.

AMPOXIN 1g

Ampicillin and Cloxacillin for Injection is White to almost white free flowing powder with creamish hue filled in 10 ml glass vial, plugged with grey butyl rubber stopper and sealed with red aluminum seal.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable.

8.2 Shelf-life

Do not use later than date of expiry.

8.3 Packaging information

AMPOXIN is available in single dose vial.

8.4 Storage and handing instructions

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

Do not allow to freeze.

9. 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

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. Cloxacillin for Injection is given intravenously, intramuscularly, or through intravenous infusion.)

It is used for

- Respiratory tract infections
- Stomach infection

- Urinary Tract Infections
- fever associated with Bacterial infection
- Blood poisoning, caused by bacteria and inflammation of the endocardium.

9.2 What you need to know before you take AMPOXIN

Do not use AMPOXIN if:

You are allergic to cloxacillin, penicillin, or cephalosporin medication.

WARNINGS AND PRECAUTIONS

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

- Kidney problems
- Liver problems
- Had allergic reactions before (Skin rash, itching etc.)
- been taking corticosteroid medication
- been taking immunosuppressant medication
- Or are pregnant or planning a pregnancy
- Blood related disorder/disease

INTERACTIONS WITH THIS MEDICATION

Drugs that may interact with Ampoxin include:

- Probenecid
- Allopurinol
- Aminoglycoside

Talk to your doctor or pharmacist about any other herbs or vitamin supplements you may be taking.

9.3 How to take AMPOXIN

Always take this medicine under the supervision of your doctor/physician.

• If you are taking this medicine for a long time, your doctor will want to monitor you.

• 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 the exact dose and duration.

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:

Ampoxin may cause some side effects such as nausea, vomiting, gastrointestinal discomfort, gas, and diarrhea.

Allergic reaction (including skin redness, rash, sneezing, swelling and trouble breathing).

Weakness, weight loss, general malaise (due to problems with white or red blood cells)

Difficulty in hearing

Abnormal liver and renal function tests

Disturbances in blood count like decrease in WBC count, RBS count or platelet count.

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.

Do not allow to freeze.

9.6 Contents of the pack and other information

What AMPOXIN contains

• The active substances are as below:

AMPOXIN 250

Each vial contains:

Ampicillin Sodium I.P. 125 mg

Cloxacillin Sodium I.P. 125 mg

AMPOXIN 500

Each vial contains:

Ampicillin Sodium I.P. equivalent to Anhydrous Ampicillin 250 mg

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

AMPOXIN 1g

Each vial contains:

Ampicillin Sodium I.P. equivalent to Anhydrous Ampicillin 500 mg

Cloxacillin Sodium I.P. equivalent to Cloxacillin 500 mg

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 250mg, 500mg, 1g Injection /APR-2020/01/PI