1 Name of the medicinal product:

Ipiclav-625mg (Amoxicillin and Clavulanate Potassium Tablets USP)

2. Qualitative and quantitative Composition:

Each film coated tablet contains: Amoxicillin
Trihydrate USP
Equivalent to Amoxicillin 500 mg
Clavulanate Potassium
Equivalent to Clavulanic Acid 125 mg

3 Pharmaceutical form:

White to off-white oval shaped film coated tablets with "R 1" embossed on one side and plain on other side.

Route of Administration: Oral

4 Clinical Particulars:

4.1 Therapeutic Indications:

Amoxicillin and clavulanate potassium combination is indicated in the treatment of infections caused by susceptible strains of the designated organisms in the conditions listed below.

Lower respiratory tract infections: Caused by ß-lactamaseproducing strains of *H. influenzae and M. catarrhalis.*

Otitis media: Caused by ß-lactamase-producing strains of *H. influenzae and M. catarrhalis.*

Sinusitis: Caused by ß-lactamase-producing strains of *H. influenzae and M. catarrhalis.*

Skin and skin structure infections: Caused by ß-lactamaseproducing strains of *S. aureus, E. coli and Klebsiella spp.*

Urinary tract infections: Caused by ß-lactamase-producing strains of*E. coli*,*Klebsiella* spp. and *Enterobacter* spp.

While amoxicillin and clavulanate potassium combination is indicated only for the conditions listed above, infections caused by ampicillin-susceptible organisms are also amenable to amoxicillin and clavulanate potassium combination treatment due to its amoxicillin content. Majority of *S. pneumoniae* strains with intermediate susceptibility to ampicillin or penicillin are fully susceptible to amoxicillin and amoxicillin and clavulanate potassium combination.

Therapy may be instituted prior to obtaining the results from bacteriological and susceptibility studies to determine the causative organisms and their susceptibility to amoxicillin and clavulanate potassium combination when there is reason to believe the

infection may involve any of the ß-lactamase producing organisms listed above. Once the results are known, therapy should be adjusted, if appropriate.

4.2 Posology and method of administration:

Amoxicillin and clavulanate potassium combination may be taken without regard to meals; however, absorption of clavulanate potassium is enhanced when amoxicillin and clavulanate potassium combination is administered at the start of a meal. To minimize the potential for gastrointestinal intolerance, the drug should be taken at the start of a meal. Duration of therapy should be appropriate to the indication and should not exceed 14 days without review.

Adults: The usual adult dose is one Rapiclav-625 tablet every 12 hours or one Rapiclav375 tablet every 8 hours. For more severe infections and infections of the respiratory tract, the dose should be one Rapiclav-1G tablet every 12 hours or one Rapiclav-625 tablet every 8 hours.

Paediatric Patients*:* Rapiclav-375, Rapiclav-625 and Rapiclav-1G tablet is suitable for paediatric patients weighing 40 Kgs or more. Paediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Usage in renal impairment: Patients with impaired renal function do not generally require a reduction in dose unless the impairment is severe. Severely impaired patients with a glomerular filtration rate of <30 mL/min. should not receive Rapiclav-1G tablet. Patients with a glomerular filtration rate of 10 to 30 ml/minute should receive Rapiclav-625 or Rapiclav- 375 tablet every 12 hours, depending on the severity of the infection. Patients with a less than 10 ml/minute glomerular filtration rate should receive Rapiclav-625 or Rapiclav-375 tablet every 24 hours, depending on severity of the infection. Hemodialysis patients should receive Rapiclav-625 or Rapiclav-375 tablet every 24 hours, depending on severity of the infection. They should receive an additional dose both during and at the end of dialysis.

Usage in hepatic impairment: Hepatically impaired patients should be dosed with caution and hepatic function monitored at regular intervals.

4.3 Contraindications:

Amoxicillin and clavulanate potassium combination is contraindicated in patients with a history of allergic reactions to any penicillin and other ingredients of the formulation. It is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with amoxicillin and clavulanate potassium combination.

4.4 Special warning and precautions for use:

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity who have experienced severe reactions when treated with cephalosporins. Before initiating therapy with amoxicillin and clavulanate potassium combination, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. If an allergic reaction occurs, amoxicillin and clavulanate potassium combination

should be discontinued and the appropriate therapy instituted. Serious anaphylactic 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 amoxicillin and clavulanate potassium combination, 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.* CDADmust be considered in all patients who present with diarrhea following antibiotic use. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.
Amoxicillin and clavulanate potassium combination should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin and clavulanate potassium combination is usually reversible. On rare occasions, deaths have been reported. These have generally been cases associated with serious underlying diseases or concomitant medications. Erythematous rashes have been associated with glandular fever in patients receiving amoxicillin.

Precautions
General
While amoxicillin and clavulanate potassium combination possesses the characteristic low toxicity of the penicillin group of antibiotics, periodic assessment of organ system functions, including renal, hepatic and hematopoietic function, is advisable during prolonged therapy.
A high percentage of patients with mononucleosis who receive ampicillin develop an erythematous skin rash. Thus, ampicillin class antibiotics should not be administered to patients with mononucleosis.
The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Pseudomonas* or *Candida*), the drug should be discontinued and/or appropriate therapy instituted.

4.5 Interaction with other medicinal products and other forms of interactions:

Probenecid decreases the renal tubular secretion of amoxicillin. Concurrent use with amoxicillin and clavulanate potassium combination may result in increased and prolonged blood levels of amoxicillin. Co-administration of probenecid cannot be recommended. The concurrent administration of allopurinol and ampicillin 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 the hyperuricemia present in these patients. There are no data with amoxicillin and clavulanate potassium combination and allopurinol administered concurrently.
In common with other broad-spectrum antibiotics, amoxicillin and clavulanate potassium combination may reduce theefficacy of oral contraceptives Amoxicillin and clavulanate potassium combination should not be used in patients receiving disulfiram. Prolongation of bleeding time and prothrombin time have been reported in some patients receiving the

amoxicillin and clavulanate potassium combination. Hence the drug should be used with care in patients on anticoagulation therapy.

4.6 Fertility, Pregnancy and lactation:

There are 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.

Ampicillin class antibiotics are excreted in the milk; therefore, caution should be exercised when amoxicillin and clavulanate potassium combination is administered to a nursing woman.

Usage in paediatrics

Efficacy and safety of amoxicillin and clavulanate potassium combination has been established even in neonates in suspension formulation. Pediatric patients weighing 40 kg or more should be dosed according to the adult recommendations.

Usage in geriatrics

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

4.7 Effect on ability to drive and use machine: None known

4.8 Undesirable effects:

Amoxicillin and clavulanate potassium combination is generally well tolerated. The most frequently reported adverse effects were diarrhea/loose stools, nausea, skin rashes and urticaria, vomiting and vaginitis. The overall incidence of side effects, and in particular diarrhea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache. The following adverse reactions have been reported for ampicillin class antibiotics:

Gastrointestinal: Diarrhea, nausea, vomiting, indigestion, gastritis, stomatitis, glossitis, black "hairy" tongue, mucocutaneous candidiasis, enterocolitis, and hemorrhagic/pseudomembranous colitis. Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment.

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, angioedema, serum sicknesslike reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia and frequently fever), erythema multiforme (rarely Stevens- Johnson Syndrome), acute generalized exanthemous pustulosis and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis) have been reported. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug should be discontinued, unless the opinion of the physician dictates otherwise. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin.

Liver:Amoderate rise inAST (SGOT) and/or ALT (SGPT) has been noted in patients treated with ampicillin class antibiotics but the significance of these findings is unknown. Hepatic dysfunction, including increases in serum transaminases (AST and/or ALT), serum bilirubin and/or alkaline phosphatase, has been infrequently reported with amoxicillin and clavulanate potassium combination. It has been reported more commonly in the elderly, in males, or in patients on prolonged treatment. The histologic findings on liver biopsy have consisted of predominantly cholestatic, hepatocellular, or mixed cholestatic-hepatocellular changes. The onset of signs/symptoms of hepatic dysfunction may occur during or several weeks after therapy has been discontinued. The hepatic dysfunction, which may be severe, is usually reversible. On rare occasions, deaths have been reported. These have generally been cases associated with serious underlying diseases or concomitant medications.

Renal: Interstitial nephritis and hematuria have been reported rarely.

Hemic and Lymphatic Systems: Anemia, including hemolytic anemia, thrombocytopenia, thrombocytopenic purpura, eosinophilia, leukopenia 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. A slight thrombocytosis was noted in less than 1% of the patients treated with amoxicillin and clavulanate potassium combination. There have been reports of increased prothrombin time in patients receiving amoxicillin and clavulanate potassium combination and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioral changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely. ***Miscellaneous***: Tooth discoloration (brown, yellow or gray staining) has been rarely reported. Most reports occurred in paediatric patients. Discoloration was reduced or eliminated with brushing or dental cleaning in most cases.

4.9 Overdose:

Following overdosage, patients have experienced primarily gastrointestinal symptoms including stomach and abdominal pain, vomiting, and diarrhea. Rash, hyperactivity, or drowsiness have also been observed in a small number of patients.

Interstitial nephritis resulting in oliguric renal failure has been reported in a small number of patients after overdosage with amoxicillin.

Crystalluria, in some cases leading to renal failure, has also been reported after amoxicillin overdosage in adult and pediatric patients. In case of overdosage, adequate fluid intake and diuresis should be mintained to reduce the risk of amoxicillin crystalluria.

Renal impairment appears to be reversible with cessation of drug administration. High blood levels may occur more readily in patients with impaired renal function because of decreased renal clearance of both amoxicillin and clavulanate.

In the case of overdosage, discontinue the drug, treat symptomatically, and institute supportive measures as required. If the overdosage is very recent and there is no contraindication, an attempt at emesis or other means of removal of drug from the stomach may be performed. A prospective study of 51 paediatric patients at a poison center suggested that overdosages of less than 250 mg/kg of amoxicillin are not associated with significant clinical symptoms and do not require gastric emptying.

Both amoxicillin and clavulanate are removed from the circulation by hemodialysis.

5. Pharmacological Properties:

5.1 Pharmacodynamic properties:

Mechanism of action

Amoxicillin is a semisynthetic antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gramnegative microorganisms. Amoxicillin is, however, susceptible to degradation by ß-lactamases. Clavulanic acid is a ß-lactam compound, tructurally related to the penicillins, which possesses the ability to inactivate a wide range of ß-lactamase enzymes commonly found in microorganisms resistant to penicillins and cephalosporins. In particular, it has good activity against the clinically important plasmidmediated ßlactamases frequently responsible for transferred drug resistance. The formulation of amoxicillin and clavulanic acid protects amoxicillin from degradation by ßlactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other ß-lactam antibiotics. Thus, the combination possesses the properties of a broad-spectrum antibiotic and a ßlactamase inhibitor.

Microbiology

Amoxicillin/clavulanic acid has been shown to be active against most strains of the following microorganisms ***Gram positive aerobes:***

Staphylococcus aureus (ß-lactamase and non-ß-lactamase producing) Staphylococci , which are resistant to methicillin/oxacillin must be considered resistant to amoxicillin/clavulanic acid.

Gram negative aerobes:

Enterobacter species (Although most strains of Enterobacter species are resistant *in vitro*, clinical efficacy has been demonstrated with amoxicillin and clavulanate the combination in urinary tract infections caused by these organisms.)

Escherichia coli (ß-lactamase and non-ß-lactamase producing).

Haemophilus influenzae (ß-lactamase and non-ß-lactamase producing).

Klebsiella species (All known strains are ß-lactamase producing).

Moraxella catarrhalis (ß-lactamase and non-ß-lactamase producing).

Amoxicillin and clavulanic acid also demonstrates *in vitro* activity against the following microorganisms but the clinical significance is unknown.

Gram positive aerobes:

- *Staphylococcus epidermidis* (ß-lactamase and non-ßlactamase producing)
- *Staphylococcus saprophyticus* (ß-lactamase and non-ßlactamase producing)
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- Viridans group Streptococcus
- *Enterococcus faecalis*

Gram negative aerobes:

- *Neisseria gonorrhoeae* (ß-lactamase and non-ßlactamase producing).
- *Proteus mirabilis* (ß-lactamase and non-ß-lactamase producing).

• *Eikenella corrodens* (ß-lactamase and non-ß-lactamase producing).

Anaerobic bacteria:

• *Bacteroides* species, including *Bacteroides fragilis* (ßlactamase and non-ß-lactamase producing).
• *Fusobacterium* species (ß-lactamase and non-ßlactamase producing).
• *Peptostreptococcus* species

5.2 Pharmacokinetic properties:

Amoxicillin and clavulanate potassium are well absorbed from the gastrointestinal tract after oral administration of amoxicillin and clavulanate potassium tablet. Dosing in the fasted or fed state has minimal effect on the pharmacokinetics of amoxicillin.

While amoxicillin and clavulanate potassium tablet can be given without regard to meals, absorption of clavulanate potassium when taken with food is greater relative to the fasted state.

Amoxicillin diffuses readily into most body tissues and fluids with the exception of the brain and spinal fluid. The results of experiments involving the administration of clavulanic acid to animals suggest that this compound, like amoxicillin, is well distributed in body tissues.

Neither component in amoxicillin and clavulanate potassium tablet is highly protein-bound; clavulanic acid has been found to be approximately 25% bound to human serum and amoxicillin approximately 18% bound.

Amoxicillin is metabolized to a limited extent to penicilloic acid. The metabolic fate of clavulanate potassium has not been fully elucidated. However, the drug appears to be extensively metabolized.

Approximately 50% to 70% of amoxicillin and approximately 25% to 40% of clavulanic acid are excreted unchanged in the urine during the first 6 hours after administration of single amoxicillin and clavulanate potassium 375 or 625 mg tablet. The half-life of amoxicillin after the oral administration of amoxicillin and clavulanate potassium is 1.3 hours and that of clavulanic acid is 1.0 hour.

5.3 Preclinical safety data:

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6. Pharmaceutical Particulars:

6.1 List of excipients:

Granulation:
Colloidal Silicon Dioxide BP
Croscarmellose Sodium BP
Microcrystalline Cellulose BP
Magnesium Stearate BP

Film Coating:
Hydroxy Propyl Methyl Cellulose BP
Dibutyl Phthalate BP

Purified talc BP
Titanium dioxide BP
Isopropyl Alcohol BP Methylene
Chloride USNF

6.2 Incompatibilities:

No incompatibilities are known

6.3 Shelf – life:

24 months

6.4 Special precautions for storage:

Store below 30°C, in a dry place, away from light.

6.5 Nature and contents of container:

Strip of 2 tablets, 7 such strips in a printed showbox along with leaflet.

6.6 Special precautions for disposal and other handling:

No specific requirement.

7. Marketing authorization holder:

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400 067, India.
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E-mail: ipca@ipca.com

8. Marketing authorization numbers:

FDA/SD.203.1193

9. Date of first authorization/renewal of authorization:

11/6/2020

10. Date of revision of the text:

08/2025