1.3 PRODUCT INDORMATION

1.3.1 Summary of Product Characteristics (SmPC)

-------Attached--------

SUMMARY OF PRODUCT CHARACTERISTICS

1.0 Name of the Medicinal Product:

Strength: (Amoxicillin 500mg and Clavulanate Potassium 125mg) /Tablet

Pharmaceutical Dosage Form: Oral Solid dosage form (Film-coated tablet)

2.0 QUALITATIVE AND QUANTITATIVE COMPOSITIONS:

Qualitative Declaration

Each film coated tablet contains:

Amoxicillin USP (as Trihydrate)

Eq. to Amoxicillin 500mg

Clavulanate Potassium USP

Eq. to clavulanic acid 125mg

3.0 PHARMACEUTICAL FORM

Oral Solid dosage form (Film-coated tablet)

4.0 CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin and Clavulanate Potassium Tablets is indicated for the treatment of the following infections in adults and children

- Acute bacterial sinusitis (adequately diagnosed)
- Cystitis
- Pyelonephritis
- Cellulitis
- Animal bites
- Severe dental abscess with spreading cellulitis.

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

4.2 Posology and method of administration

Posology

Doses are expressed throughout in terms of amoxicillin/clavulanic acid content except when doses are stated in terms of an individual component.

The dose of Amoxicillin and Clavulanate Potassium Tablets that is selected to treat an individual infection should take into account:

• The expected pathogens and their likely susceptibility to antibacterial agents.
• The severity and the site of the infection
• The age, weight and renal function of the patient as shown below.

The use of alternative presentations of Amoxicillin and Clavulanate Potassium Tablets (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary.

For adults and children ≥ 40 kg, this formulation of Amoxicillin and Clavulanate Potassium Tablets provides a total daily dose of 750 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Amoxicillin and Clavulanate Potassium Tablets is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

Treatment should not be extended beyond 14 days without review.

Adults and children ≥ 40 kg

One tablet taken three times a day.

Children < 40 kg

Amoxicillin and Clavulanate Potassium Tablets 250 mg/125 mg film-coated tablets are not recommended in children < 40 kg.

Elderly

No dose adjustment is considered necessary.

Renal impairment

Dose adjustments are based on the maximum recommended level of amoxicillin.

No adjustment in dose is required in patients with creatinine clearance (CrCl) greater than 30 ml/min.

Adults and children ≥ 40 kg

CrCl: 10-30 ml/min	250 mg/125 mg twice daily
CrCl < 10 ml /min	250 mg/125 mg once daily
Haemodialysis	Two doses of 250 mg/125 mg every 24 hours, plus two doses of 250 mg/125 mg during dialysis, to be repeated at the end of dialysis (as

	serum concentrations of both amoxicillin and clavulanic acid are decreased)

Children < 40 kg

In children < 40 kg with creatinine clearance less than 30 ml/min, the use of Amoxicillin and Clavulanate Potassium Tablets presentations with an amoxicillin to clavulanic acid ratio of 2:1 is not recommended, as no dose adjustments are available. In such patients, Amoxicillin and Clavulanate Potassium Tablets formulations with an amoxicillin to clavulanic acid ratio of 4:1 are recommended.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals.

Method of administration

Amoxicillin and Clavulanate Potassium Tablets is for oral use.

Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.

4.3 Contraindications:

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients.

History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. a cephalosporin, carbapenem or monobactam).

History of jaundice/hepatic impairment due to amoxicillin/clavulanic acid.

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.

Serious and occasionally fatal hypersensitivity (anaphylactoid) 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 in atopic individuals. If an allergic reaction occurs, amoxicillin/clavulanic acid therapy must be discontinued and appropriate alternative therapy instituted

4.5 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in

patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

Methotrexate

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

Probenecid

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use of probenecid may result in increased and prolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil

In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of the active metabolite mycophenolic acid (MPA) of approximately 50% has been reported following commencement of oral amoxicillin plus clavulanic acid. The change in pre-dose level may not accurately represent changes in overall MPA exposure.

4.6 Pregnancy and lactation

Pregnancy

Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations.

Breastfeeding

Both substances are excreted into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucous membranes are possible in the breast-fed infant, so that breast-feeding might have to be discontinued.

Fertility

Information not available

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The most commonly reported side effect of amoxicillin/clavulanate is diarrhea, often associated with abdominal cramps, with a reported incidence of 2.9 percent to 14.5 percent. Nausea (2.1 percent to 3 percent), vomiting (1 percent to 2.2 percent) and rash (1.1 percent to 3 percent) are also common side effects.

This can occur up to several weeks after treatment with an antibiotic and is, in the U.S., frequently associated with a toxin produced by Clostridium difficile. Some cases respond to discontinuation of the antibiotic, but often treatment with an antibiotic effective against C-difficile is necessary.

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.

In the case of overdosage, discontinue amoxicillin/clavulanate potassium, 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors;

ATC code: J01CR02.

Mechanism of action

Amoxicillin is semi synthetic penicillin (beta-lactam antibiotic) that inhibits one or more enzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathway of bacterial peptidoglycan, which is an integral structural component of the bacterial cell wall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which is usually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteria and therefore the spectrum of activity of amoxicillin alone does not include organisms which produce these enzymes.

Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some beta-lactamase enzymes thereby preventing inactivation of amoxicillin. Clavulanic acid alone does not exert a clinically useful antibacterial effect.

Pharmacodynamic effects

The time above the minimum inhibitory concentration (T>MIC) is considered to be the major determinant of efficacy for amoxicillin.

Mechanisms of resistance

The two main mechanisms of resistance to amoxicillin/clavulanic acid are:

• Inactivation by those bacterial beta-lactamases that are not themselves inhibited by clavulanic acid, including class B, C and D.

• Alteration of PBPs, which reduce the affinity of the antibacterial agent for the target.

Impermeability of bacteria or efflux pump mechanisms may cause or contribute to bacterial resistance, particularly in Gram-negative bacteria.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. Following oral administration, amoxicillin and clavulanic acid are approximately 70% bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (250 mg/125 mg tablets three times daily) was administered in the fasting state to groups of healthy volunteers, are presented below.

Mean (± SD) pharmacokinetic parameters					
Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	AUC $_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 250 mg/125 mg	250	3.3 ± 1.12	1.5 (1.0-2.0)	26.7±4.56	1.36 ± 0.56
Clavulanic acid					
AMX/CA	125	1.5	1.2	12.6	1.01

250 mg/125 mg		± 0.70	(1.0-2.0)	± 3.25	± 0.11
AMX – amoxicillin, CA – clavulanic acid * Median (range)					

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.

Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk.

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

The major route of elimination for amoxicillin is via the kidney, whereas for clavulanic acid it is by both renal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h after administration of single Amoxicillin and Clavulanate Potassium Tablets. Various studies have found the urinary excretion to be 50-85% for amoxicillin and between 27-60%

for clavulanic acid over a 24 hour period. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours after administration.
Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid.

Age

The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and older children and adults. For very young children (including preterm newborns) in the first week of life the interval of administration should not exceed twice daily administration due to immaturity of the renal pathway of elimination. 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.

Gender

Following oral administration of amoxicillin/clavulanic acid to healthy males and female subjects, gender has no significant impact on the pharmacokinetics of either amoxicillin or clavulanic acid.

Renal impairment

The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a higher proportion of amoxicillin is excreted *via* the renal route. Doses in renal impairment must therefore prevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid.

Hepatic impairment

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

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.
Repeat dose toxicity studies performed in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.
Carcinogenicity studies have not been conducted with amoxicillin/clavulanic acid or its components.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Name of components	Reference
Microcrystalline Cellulose PH-112	BP
Croscarmellose sodium	BP
Crospovidone	BP
Sodium Starch Glycolate	BP
Colloidal anhydrous silica	BP
Purified talc	BP
Magnesium stearate	BP
Sodium Lauryl Sulfate	BP
DRCOAT MB - S	IH
Isopropyl alcohol	BP
Dichloromethane	BP
Titanium Dioxide	BP

6.2 Incompatibilities

Not applicable.

6.3 Shelf – life:

36 months from the date of manufacturing.

6.4 Special precautions for storage:

Do not store above 30°C

6.5 Nature and contents of container:

7 tablets are packed in Alu-Alu blister.

2 blisters packed with LDPE pouch in carton along with package insert, 5 mono carton placed in outer carton.

7. Marketing authorisation holder

BISISTA PHARMA PVT. LTD.

INDIA

8. Marketing authorisation number(s):

===NA===

9. Date of first authorisation/renewal of the authorisation:

===NA===

10. Date of revision of the text:

===NA===

11. Date of revision of the text

===NA===