1.3.1 SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT:

NECTACLAV TABLET (AMOXICILLIN & CLAVULANATE POTASSIUM TABLET USP)

2. QUALITATIVE & QUANTITATIVE COMPOSITION

Qualitative Declaration

Each Film Coated Tablets Contains:

Amoxicillin Trihydrate USP

Equivalent to Amoxicillin……...500mg

Clavulanate Potassium USP

Equivalent to Clavulanic Acid ……125mg

Excipients……Q.S.

Colour: Titanium Dioxide

Quantitative Declaration

Batch Size: 1,00,000 Tablets

Sr. No	Name of Raw Material	Spec	% Overage	Input (mg/tab)	Std. Qty for 1 Lac	UOM	Req. Qty/ batch
1.	*Amoxicillin Trihydrate (Extra dry) (compacted)	USP	3%	590.0	59.000	Kg	59.000
2.	Potassium Clavulanate (Avicel)	USP	5%	305.0	30.500	Kg	30.500
3.	Syloid 244 FP	USP		52.000	5.200	Kg	5.200
4.	Sodium Starch Glycolate	BP		20.000	2.000	Kg	2.000
5.	Ac-di-sol	BP		15.00	1.500	Kg	1.500
6.	Aerosil (Colloidal Silicon Dioxide)	BP		7.000	0.700	Kg	0.700
7.	MCC RQ 102	BP		33.000	3.300	Kg	3.300
8.	Magnesium Stearate	BP		8.00	0.800	Kg	0.800
Coating Material							
9.	Ethyl Cellulose	BP		8.00	0.800	Kg	0.800
10.	Isopropyl Alcohol	BP		93.458	9.345	Lit.	9.345
11.	Insta coat solution ICS223 WHITE	IH		30.00	3.000	Kg	3.000
12.	Methylene Dichloride			342.056	34.205	Lit.	34.205
13.	Isopropyl Alcohol	BP		228.037	22.803	Lit.	22.803
14.	Diethyl Phthalates	BP		7.000	0.700	Kg	0.700

3. PHARMACEUTICAL FORM

White coloured capsule shaped, film coated tablets break line on one side and plain on other side.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

NECTACLAV is indicated in the treatment of infection caused by susceptible strains of the organisms in the conditions listed below.

Upper Respiratory Tract Infections e.g. Tonsillitis sinusitis, otitis media.

Lower Respiratory Tract Infections e.g. Acute and chronic lobar and Bronchopneumonia

Genito-Urinary Tract Infections e.g. Cystitis, urethritis, pyelonephritis.

Skin and Soft Tissue Infections e.g. Boils/abscesses, cellulitis, wound infections.

Bone and Joint Infections e.g. Osteomyelitis.

Other Infections e.g. Intra-abdominal sepsis.

While **NECTACLAV** is indicated for above-mentioned conditions, infections caused by ampicillin-susceptible organisms are also amenable to **NECTACLAV** treatment due to its amoxicillin content. Therefore, mixed infections caused by ampicillin susceptible organisms and β-lactamase producing organisms susceptible to **NECTACLAV** should not require the addition of another antibiotic.

Bacteriology:

AMOXICILLIN is a B-lactam antibiotic with a broad spectrum of bactericidal activity against many gram-positive and gram negative micro-organism, Amoxicillin is however susceptible to degradation by B-lactamase & therefore the spectrum of activity does not include organisms which produce these enzymes.

CLAVULANIC ACID is a B-lactamase inhibitor structurally related to the penicillins, which possesses the ability to inactivate a wide range of B-lactamase enzymes commonly found in micro-organisms resistant to penicillin & cephalosporins. In particular, it has good activity against the clinically important plasmid mediated p-lactamases frequently responsible for drug resistance. The combination of amoxicillin and clavulanic acid in NECTACLAV protects amoxicillin from degradation by B-lactamase enzymes and effectively extends the antibiotic spectrum of amoxicillin to include many bacteria normally resistant to amoxicillin and other B-lactam antibiotics.

Thus, **NECTACLAV** possesses the distinctive properties of a broad-spectrum antibiotic and a β-lactamase inhibitor.

NECTACLAV is active against a wide range of gram-positive and gram-negative bacteria including many clinically important β-lactamase producing penicillin-resistant organisms both in the hospital and general practice including:

GRAM-POSITIVE

Aerobes: Enterococcus faecalis Coagulase-negative staphylococci including

Streptococcus pneumoniae Staphylococcus epidermidis*

Streptococcus pyogenes Corynebacterium species

Streptococcus aureus* Bacillus anthracis

Listeria monocytogenes

Anaerobes: Clostridium species Peptococcus species Peptostreptococcus

GRAM-NEGATIVE

Aerobes: Haemophilus influenza Klebsiella species* Neisseria gonorrhoeae

Escherichia coli* Salmonella species* Neisseria meningitidis

Moraxella catarrhalis* Shigella species* Vibrio Cholerae

Proteus mirabilis* Bordetella pertussis Pasteurella multocida

Proteus vulgaris* Brucella Species

Anaerobes: Bacteroides spp. Including B. fragilis*

*including B-lactamase producing strains resistant to ampicillin and amoxicillin.

4.2 Dosage and administration:

In pediatric patients, based on the amoxicillin component **NECTACLAV** should be dosed as follows:

Neonates and Infants aged < 12 weeks (3 months): Due to incompletely developed renal function affecting elimination of amoxicillin in this age group, the recommended dose of **NECTACLAV** is 30mg/kg/day divided 12 hrly, based on the amoxicillin component, clavulanate elimination is unaltered in this age group. Experience with the 200 mg / 5 ml formulation in this age group is limited and thus use of the 125mg/5ml oral suspension is recommended.

Children aged up to 2 years: children under 2 years should be dosed according to body weight.

Pediatric patients weighing 40 kg and more: Should be dosed according to the following adult recommendations.

Children from 3 months and older (body weight is less than 40 kg):

For Adults: The usual adult dose is **NECTACLAV 625** mg tablets every 12 hours. For more severe infections and infections of the respiratory tract, the dose should be **NECTACLAV 625** mg tablets every 8 hours. The 12 hrly regimen is recommended as it is associated with significantly less diarrhoea. Duration of therapy studied and, recommended for acute otitis media is 10 days.

Infants with immature kidney function: For children with immature renal function **NECTACLAV** is not recommended.

Renal Impairment: For children with GFR of >30 ml/min adjustment in dosage is required. Adult patients with impaired renal function do not generally require reduction in dose unless the impairment is severe. Patient with a GFR of 10 to 30 ml/min should receive **NECTACLAV 625** every 12 hrs and patient with a GFR <10 ml/min should receive **NECTACLAV 625** every 24 hrs, depending on severity of the infection.

Haemodialysis patient should receive **NECTACLAV 625** every 24 hrs, depending on the severity of the infection. They should receive an additional dose during and at the end of dialysis.

Hepatic impairment: Dose with caution, monitor hepatic function at intervals. There is, as yet, insufficient evidence on which to base a dosage recommendation.

4.3 Contraindications:

Amoxicillin + clavulanic acid is contraindicated in patients with a history of allergic reactions to any penicillins. It is also contraindicated in patients with a history of amoxicillin + clavulanic acid associated cholestatic jaundice/ hepatic dysfunction.

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 reactions (including anaphylactoid and severe cutaneous adverse 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 should be discontinued and appropriate alternative therapy instituted.

In the case that an infection is proven to be due to an amoxicillin-susceptible organisms(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Co-amoxiclav may not be suitable for use when there is a high risk that the presumptive pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. As no specific data for T>MIC are available and the data for comparable oral presentations are borderline, this presentation (without additional amoxicillin) may not be suitable for the treatment of penicillin-resistant S. pneumoniae.

Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.

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

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) .This reaction requires Co-amoxiclav discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been very rarely reported in children. In all populations, signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until several weeks after treatment has ceased. These are usually reversible. Hepatic events may be severe and in extremely rare circumstances, deaths have been reported. These have almost always occurred in patients with serious underlying disease or taking concomitant medications known to have the potential for hepatic effects.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening .Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibiotics. Should antibiotic-associated colitis occur, Co-amoxiclav should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic drugs are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic function is advisable during prolonged therapy.

Prolongation of prothrombin time has been reported rarely in patients receiving amoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation .In patients with renal impairment, the dose should be adjusted according to the degree of impairment

In patients with reduced urine output crystalluria has been observed very rarely, predominantly with parenteral therapy.

During administration of high doses of amoxicillin it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained

During treatment with amoxicillin, enzymatic glucose oxidase methods should be used whenever testing for the presence of glucose in urine because false positive results may occur with non-enzymatic methods.

The presence of clavulanic acid in Co-amoxiclav may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

There have been reports of positive test results using the Bio-Rad Laboratories Platelia Aspergillus EIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free of Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously and confirmed by other diagnostic methods.

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

Penicillin's 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. A change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. Close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

4.6 Fertility, 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. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

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 breastfeeding might have to be discontinued. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effects on Ability to Drive and Use Machines:

No studies on the effects on the ability to drive and use machines have been performed. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines

4.8 Undesirable Effects

Amoxicillin and Clavulanate Potassium is generally well tolerated. The majority of side effects observed in clinical trials were of a mild and transient nature and less than 3 % of patients discontinued therapy because of drug - related side effects. From the original premarketing studies, where both pediatric and adult patients were enrolled, the most frequently reported adverse effects were diarrhoea / loose stools (9 %), nausea (3 %), skin rashes and urticaria (3 %), vomiting (1 %) and vaginitis (1 %). The overall incidence of side effects, and in particular diarrhoea, increased with the higher recommended dose. Other less frequently reported reactions include: abdominal discomfort, flatulence and headache.

In pediatric patients (aged 2 months to 12 years), one U.S. / Canadian clinical trial was conducted which compared Amoxicillin and Clavulanate Potassium 45 / 6.4 mg / kg / day (divided q12h) for 10 days versus Amoxicillin and Clavulanate Potassium 40 / 10 mg / kg / day (divided q8h) for 10 days in the treatment of acute otitis media. A total of 575 patients were enrolled, and only the tablet formulations were used in this trial. Overall, the adverse event profile seen was comparable to that noted above. However, there were differences in the rates of diarrhea, skin rashes / urticaria, and diaper area rashes.

The following adverse reactions have been reported for ampicillin class antibiotics:

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

Hypersensitivity Reactions: Skin rashes, pruritus, urticaria, and angioedema, serum sickness - like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, and myalgia and frequently fever), erythema multiforme (rarely Stevens - Johnson syndrome) 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 A moderate rise in AST (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. 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 (less than 1 death reported per estimated 4 million prescriptions worldwide). 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 Augmentin. There have been reports of increased prothrombin time in patients receiving Amoxicillin and Clavulanate Potassium and anticoagulant therapy concomitantly.

Central Nervous System: Agitation, anxiety, behavioural changes, confusion, convulsions, dizziness, insomnia, and reversible hyperactivity have been reported rarely.

4.9 Overdose

Problem of overdosage with **NECTACLAV** are unlikely to occur, if encountered they may be treated symptomatically **NECTACLAV** may be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors; **ATC code**: J01CR02.

Mechanism of action

Amoxicillin is a semisynthetic 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.

PK/PD relationship

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

The pharmacokinetic results for studies in which amoxicillin/clavulanic acid was administered to groups of healthy volunteers as either 500 mg/100 mg or 1000 mg/200 mg given as a bolus intravenous injection are presented below.

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 (see section 4.6).

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 a single 500/100 mg or a single 1000/200 mg bolus intravenous injection. 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

5.3 Preclinical safety data

Not applicable

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS:

Syloid 244 FP
Sodium Starch Glycolate
Ac-di-sol
Aerosil (Colloidal Silicon Dioxide)
MCC RQ 102
Magnesium Stearate
Ethyl Cellulose
Isopropyl Alcohol
Insta coat solution ICS223 WHITE
Methylene Dichloride
Isopropyl Alcohol
Diethyl Phthalates

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

24 Months

6.4 Special Precautions for Storage

Stored at temperature below 30°C in a dry place. Protect from light.

6.5 Nature and Contents of Container

2 X 7 Tablets of Alu- Alu Blister pack

6.6 Special Precautions for Disposal of a used medicinal product or waste materials derived from such medicinal product and Other Handling of the Product

No special requirements

7. APPLICANT/HOLDER OF CERTIFICATE OG PRODUCT REGISTRATION

Nectar Healthcare Ltd.

16B Residence Street, Gbagada Estate, Phase 2, Gbagada Lagos.

8. DRUG PRODUCT MANUFACTURER

VAPI CARE PHARMA PVT LTD

Plot No 225/3, Nr. Morarji Circle, G.I.D.C, Vapi, Dist- Valsad – 396195.

9. NAFDAC REGISTRATION NUMBER(S)

A4-9508