SUMMARY OF PRODUCT CHARACTERISTICS

1. **NAME OF THE FINISHED PHARMACEUTICAL PRODUCT**

Proprietary name: **CLAVOPIL 228.5**

Generic Name: **Amoxicillin and Clavulanate Potassium for Oral Suspension USP 228.5 mg (5ml)**

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

Label claim:

After reconstitution Each 5 ml contains:

Amoxicillin USP (As Trihydrate) eq. to Amoxicillin 200 mg

Clavulanate Potassium USP eq. to Clavulanic Acid 28.5 mg

List of Excipients:

Mannitol, Sodium citrate, Citric Acid Monohydrate, Sodium Benzoate, Xanthan Gum, Colloidal Silicon Dioxide, Aspartame, Flavour Capsil cloudifying, Flavour strawberry.

3. **PHARMACEUTICAL FORM**

3) PHARMACEUTICAL FORM	**:**	
Dosage Form	:	Powder For Oral Suspension (Dry Syrup)
Usage (oral, injection & etc)	:	For oral administration
Description	:	A white to creamish granular powder filled in 70 ml HDPE Plastic bottle, after reconstitution with water it gives creamish colored homogenous suspension with strawberry flavour.

4. **CLINICAL PARTICULARS**

4.1 THERAPEUTIC INDICATIONS

CLAVOPIL 228.5 is indicated for the treatment of the following bacterial infections when amoxicillin resistant β-lactamase producing strains are suspected as the cause. In other situations, amoxicillin alone should be considered:

Upper respiratory tract infections (including ENT): recurrent tonsillitis, acute sinusitis, acute otitis media;

Lower respiratory tract infections: acute exacerbations of chronic bronchitis, community-acquired pneumonia;

Urinary tract infections: cystitis (especially when recurrent or complicated - excluding prostatitis), pyelonephritis;

Skin and soft tissue infections: cellulitis, animal bites and severe dental abscess with spreading cellulitis;

Other infections: septic abortion, puerperal sepsis, Intra-abdominal sepsis. Consideration should be given to official guidance on the appropriate use of antibacterial agents..

4.2 Posology and method of administration

Adults and Children over 12 years

Mild - Moderate Infections	One CLAVOPIL 375 tablet thrice a day or One CLAVOPIL 625 tablet twice a day
Severe infections	One CLAVOPIL 1000 tablet twice a day

Children 12 years and below:

CLAVOPIL 156.25 [Amoxicillin and Clavulanate Potassium For Oral Suspension USP 156.25 mg (5 ml)]	Children 1-6 years (10-18 kg): 5 ml every 8 hours Or 0.8 ml/kg daily in 3 divided doses.

CLAVOPIL 228.5 [Amoxicillin and Clavulanate Potassium For Oral Suspension USP 228.5 mg (5 ml)]	Children 6-12 years (18-40 kg): 5 ml every 8 hours Or 0.4 ml/kg daily in 3 divided doses.

CLAVOPIL DRY POWDER 312.5 MG / 5 ML [Amoxicillin and Clavulanate Potassium For Oral Suspension USP 312.5 mg (5 ml)]	Children 6-12 years (18-40 kg): 5 ml every 8 hours Or 0.4 ml/kg daily in 3 divided doses.

CLAVOPIL DRY POWDER 457 MG / 5 ML [Amoxicillin and Clavulanate Potassium For Oral Suspension USP 457 mg (5 ml)]	Children 6-12 years (18-40 kg): 2.5 ml every 8 hours Or 0.2 ml/kg daily in 3 divided doses.

In severe infections, the dose may be increased depending on the severity.

CLAVOPIL tablets are not recommended in children of 12 years and under due to lack of safety data.

Dosage in Renal Impairment:

Adults and Children over 12 years:

Mild impairment (Creatinine clearance > 30 ml/min): No change in dosage.

Moderate impairment (Creatinine clearance 10-30 ml/min): One CLAVOPIL 375 tablet or one CLAVOPIL 625 tablet every 12 hours.

Severe impairment (Creatinine clearance < 10 ml/min): Not more than one CLAVOPIL 375 tablet every 24 hours. CLAVOPIL 625 tablet & CLAVOPIL 1000 tablet are not recommended.

Children 12 years and below:

For children with a GFR of >30 ml/min no adjustment in dosage is required.

Dosage in Hepatic impairment:

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

Elderly

No adjustment needed; dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults.

METHOD OF ADMINISTRATION: Tap the bottle to loosen the Powder. Slowly add pre-boiled, cold water upto the arrow mark on the label. Shake vigorously.

Adjust the volume up to the arrow mark on the label adding more water, if necessary. This makes 70 ml of the suspension.

Store the reconstituted suspension in refrigerator when not in use.

Use the reconstituted suspension within 7 days.

Shake well before use

4.3 Contraindications

CLAVOPIL is contraindicated:

In patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins and to any of the excipients.

In patients with a previous history of CLAVOPIL associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

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

Before initiating therapy with CLAVOPIL, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, or other allergens.

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.

Change in liver function tests have been observed in some patients receiving CLAVOPIL. The clinical significance of these changes is uncertain but CLAVOPIL should be used with caution in patients with evidence of hepatic dysfunction.

Cholestatic jaundice, which may be severe, but is usually reversible, has been reported rarely. Signs and symptoms may not become apparent for several weeks after treatment has ceased.

In patients with renal impairment, dosage should be adjusted according to the degree of impairment.

CLAVOPIL should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilli form rash has been associated with this condition following the use of amoxicillin.

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

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Prolongation of bleeding time and prothrombin time have been reported in some patients receiving CLAVOPIL. CLAVOPIL should be used with care in patients on anti-coagulation therapy.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of CLAVOPIL and allopurinol.

In common with other antibiotics, CLAVOPIL may affect the gut flora, leading to lower oestrogen re absorption and reduced efficacy of combined oral contraceptives.

4.6 Fertility, pregnancy and lactation

This product should only be used in pregnancy or lactation if considered essential by the physician.

Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered amoxicillin-clavulanate have shown no teratogenic effects.

In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with amoxicillin-clavulanate may be associated with an increased risk of necrotising enterocolitis in neonates.

CLAVOPIL may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

4.7 Effects on ability to drive and use machines

CLAVOPIL has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Data from large clinical trials was used to determine the frequency of very common to rare undesirable effects. The frequencies assigned to all other undesirable effects (i.e., those occurring at <1/10,000) were mainly determined using post-marketing data and refer to a reporting rate rather than a true frequency. The following convention has been used for the classification of frequency:

very common >1/10common >1/100 and <1/10uncommon >1/1000 and <1/100rare >1/10,000 and <1/1000very rare <1/10,000.

Infections and infestations

Common: Mucocutaneous candidiasis

Blood and lymphatic system disorders

Rare: Reversible leucopenia (including neutropenia) and thrombocytopenia

Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time

Immune system disorders

Very rare: Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system disorders

Uncommon: Dizziness, headache

Very rare: Reversible hyperactivity and convulsions. Convulsions may occur in patients with impairedrenal function or in those receiving high doses.

Gastrointestinal disorders

Very common: Diarrhoea

Common: Nausea, vomiting

Uncommon: Indigestion

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagiccolitis), black hairy tongue.

Hepatobiliary disorders

Uncommon: A moderate rise in AST and/or ALT and alkaline phosphatases has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown.

Very rare: Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins.

Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

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.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash, pruritus, urticariaRare: Erythema multiforme

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acutegeneralised exanthemous pustulosis (AGEP)

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Renal and urinary disorders

Very rare: Interstitial nephritis, crystalluria

4.9 Overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance. CLAVOPIL can be removed from the circulation by haemodialysis. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: β-lactam antibacterials, combination of penicillin and beta-lactamase inhibitor ATC code: J0ICR02

Mode of action

Amoxicillin is a semisynthetic penicillin 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 that is usually followed by cell lysis and bacterial death. Clavulanic acid is a beta-lactam agent structurally related to penicillins that can inactivate certain (but not all) beta-lactamase enzymes manufactured by bacteria and so can prevent enzymic degradation of amoxicillin.

Pharmacokinetic/Pharmacodynamic Relationship

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

Mechanisms of resistance

There are two main mechanisms of resistance to beta-lactam antibiotics, i.e. target (PBP) alteration and inactivation by beta-lactamases. Less often impermeability or eflux pump mechanisms may cause or contribute to bacterial resistance.

Breakpoints

MIC breakpoints for Amoxiclav shown below are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST) except for Staphylococci, for which there are no EUCAST MIC breakpoints and therefore those recommended by the Clinical and Laboratory Standards Institute (CLSI; 2008) are given.

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant
Streptococcus pneumoniae	<0.5	1-2	>2
Haemophilus influenzae	<1	-	>1
Staphylococcus spp.	<4	-	>8
Enterobacteriaceae	-	-	>8

1. The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of Clavulanic acid is fixed at 2 mg/1
2. Break point values in the table are based on ampicillin breakpoints.
3. CLSI breakpoints (no intermediate value is specified). Staphylococci which are susceptible to amoxicillin/Clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.
4. The resistant break point of R>8 mg/L ensures that all isolates with resistance mechanisms are reported resistant.

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

CLAVOPIL is bactericidal to a wide range of organisms including:

Gram-positive aerobes:

Bacillus anthracis #

Corynebacterium speciesEnterococcus faecalis#

Enterococcus faecium#

Listeria monocytogenesNocardia asteroides Staphylococcus aureus#

Coagulase negative staphylococci# (including Staphylococcus epidermidis#)

Streptococcus agalactiae

Streptococcus pneumoniae

Streptococcus pyogenes

Streptococcus species

Streptococcus viridans

Gram-negative aerobes:

Bordetella pertussis Brucella species Escherichia colt#

Gardnerella vaginalis

Haemophilus influenzae#Helicobacter pyloriKlebsiella species#

Legionella species

Moraxella catarrhalis# (Branhamella catarrhalis)

Neisseria gonorrhoeae#

Neisseria meningitidis#

Pasteurella multocida

Proteus mirabilis#

Proteus vulgaris#

Salmonella species#

Shigella species#

Vibrio cholerae

Yersinia enterocolitica#

Gram-positive anaerobes:

Clostridium species

Peptococcus species

Peptostreptococcus species

Gram-negative anaerobes:

Bacteroides species# (including Bacteroides fragilis)

Fusobacterium species#

Others:

Borrelia burgdorferiChlamydiae

Leptospira icterohaemorrhagiaeTreponema pallidum

Species for which acquired resistance may be a problem:

Gram-positive aerobes:

Enterococcus faecium#

Gram-negative aerobes:

Escherichia coli#

Klebsiella sp.#

Shigella sp.#

Salmonella sp.#

Yersinia enterocolitica#

Inherently resistant organisms:

Gram-positive aerobes:

Methicillin-resistant staphylococci (MRSA/MRSE)

Gram-negative aerobes:

Pseudomonas sp.

Stenotrophomonas multophiliaAcinetobacter spp.

Serratia spp.

Some members of these species of bacteria produce beta-lactamase and are therefore insensitive to amoxicillin alone.

5.2 Pharmacokinetic properties

Absorption

The two components, of CLAVOPIL, 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 CLAVOPIL is optimised when taken at the start of a meal.

Distribution

Following i.v. administration, therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor Clavulanic acid is highly protein bound, studies show that about 25% for Clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein.

From animal studies there is no evidence to suggest that either component accumulates in any organ.

CLAVOPIL, like most penicillins, can be detected in breast milk. Trace quantities of clavulanate can also be detected in breast milk. With the exception of the risk of sensitisation associated with this excretion, there are no known detrimental effects for the breast-fed infant.

Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the fetus was detected.

Metabolism

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-lH-pyrrole-3-carboxylic acid and l-amino-4-hydroxy-butan-2-one and eliminatedin urine and feces as carbon dioxide in expired air.

Elimination

As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate it is by both renal and non-renal mechanisms. Approximately 60 to 70% of the amoxicillin and approximately 40 to 65% of the Clavulanic acid are excreted unchanged in urine dining the first 6 h after administration of a single 250/125 mg or a single 500/125 mg tablet.

Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of Clavulanic acid .

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on studies of safety pharmacology, repeated dose toxicity and toxicity to reproduction. Carcinogenicity studies have not been conducted with CLAVOPIL or its components. However, potassium clavulanate alone or combined 1:2 or 1:4 with amoxicillin has been tested in a comprehensive battery of in vitro and in vivo genotoxicity tests which showed no significant genotoxic hazard.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

1) Mannitol
2) Sodium citrate
3) Citric Acid Monohydrate
4) Sodium Benzoate
5) Xanthan Gum
6) Colloidal Silicon Dioxide
7) Aspartame
8) Flavour Capsil cloudifying
9) Flavour strawberry

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Storage condition:

Keep container tightly closed, Store in dry place, Do not store above 25^{o}C. Keep all medicines out of sight & reach of Children.

6.5 Nature and contents of container

70 ml HDPE Plastic Bottle packed in a carton with leaflet & measuring cup.

6.6 Instructions for use and handling and disposal

No special requirements

7. **Marketing authorization holder**

Name : Appealing Healthcare & Pharmacy.

Address : 46, Abayomi Street, Oshodi, Lagos State, Nigeria.

Name and address of Manufacturer

Applicant's Name: **SPARSH BIO-TECH PVT.LTD. PHARMACEUTICAL MANUFACTURER & EXPORTERS**

Address: PLOT NO.1, SURVEY NO. 242/243/244, LAKHABAVAD, JAMNAGAR – 361 006 (INDIA)

8. **Number(s) in the national register of finished pharmaceutical products**

NAFDAC REGN. NO.:

9. **Date of first authorization/renewal of the authorization**

10. **DATE OF REVISION OF THE TEXT**