1.3 Prescribing information

1.3.1 Product information for Health Professionals (For All Products subject to Medical Prescription)

1) **NAME OF THE MEDICINAL PRODUCT:**

(a) Proprietary name : AMPLIFY 1000

Generic Name : Amoxicillin and Clavulanate Potassium Tablets USP 1000 mg

(b) Strength :

Amoxicillin USP (As Trihydrate) eq. to Amoxicillin 875 mg

Clavulanate Potassium USP eq. to Clavulanic Acid 125 mg

(c) Pharmaceutical form

Oral Solid Dosage Form (Film Coated Tablets)

2) QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each film coated tablet contains:

Amoxicillin USP (As Trihydrate) Eq. to Amoxicillin..... 875 mg

Clavulanate Potassium USP Eq. to Clavulanic Acid.....125 mg

For a full list of excipients see section 6.1.

3) PHARMACEUTICAL FORM :

Film coated tablet

White colored, Caplet shaped, biconvex, film coated tablet having plain surfaces on the both sides. The tablet should not be divided.

4) CLINICAL PARTICULARS:

4.1) THERAPEUTIC INDICATIONS :

AMPLIFY indicated for the treatment of the following infections in adults and children (see sections 4.2, 4.4 and 5.1):

• Acute bacterial sinusitis (adequately diagnosed)

• Acute otitis media

• Acute exacerbations of chronic bronchitis (adequately diagnosed)

• Community acquired pneumonia

• Cystitis

• Pyelonephritis

• Skin and soft tissue infections in particular cellulitis, animal bites, severe dental abscess with spreading cellulitis.

• Bone and joint infections, in particular osteomyelitis.

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

4.2) POSOLOGY AND METHOD OF ADMINISTRATION:

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 AMPLIFY that is selected to treat an individual infection should take into account:

- ✧ The expected pathogens and their likely susceptibility to antibacterial agents (see section 4.4)
- ✧ 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 AMPLIFY (e.g. those that provide higher doses of amoxicillin and/or different ratios of amoxicillin to clavulanic acid) should be considered as necessary (see sections 4.4 and 5.1).

For adults and children ≥ 40 kg, this formulation of AMPLIFY provides a total daily dose of 1750 mg amoxicillin/ 250 mg clavulanic acid with twice daily dosing and 2625 mg amoxicillin/375 mg clavulanic acid with three times daily dosing, when administered as recommended below. For children < 40 kg, this formulation of AMPLIFY provides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 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 AMPLIFY is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid (see sections 4.4 and 5.1).

The duration of therapy should be determined by the response of the patient. Some infections (e.g. osteomyelitis) require longer periods of treatment. Treatment should not be extended beyond 14 days without review (see section 4.4 regarding prolonged therapy).

<u>Adults and children ≥ 40 kg</u>

Recommended doses:

- ✧ standard dose: (for all indications): 875 mg/125 mg two times a day;
- ✧ higher dose - (particularly for infections such as otitis media, sinusitis, lower respiratory tract infections and urinary tract infections): 875 mg/125 mg three times a day.

<u>Children < 40 kg</u>

Children may be treated with AMPLIFY tablets or suspensions.

Recommended doses:

25 mg/3.6 mg/kg/day to 45 mg/6.4 mg/kg/day given as two divided doses;

up to 70 mg/10 mg/kg/day given as two divided doses may be considered for some infections (such as otitis media, sinusitis and lower respiratory tract infections).

As the tablets cannot be divided, children weighing less than 25 kg must not be treated with AMPLIFY tablets.

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 875 mg/125 mg tablet.

Body weight [kg]	40	35	30	25	Single dose recommended [mg/kg body weight] (see above)
Amoxicillin [mg/kg body weight] per single dose (1 film-coated tablet)	21.9	25.0	29.2	35.0	12.5 – 22.5 (up to 35)
Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet)	3.1	3.6	4.2	5.0	1.8 – 3.2 (up to 5)

Children weighing less than 25 kg should preferably be treated with AMPLIFY suspension.

No clinical data are available for AMPLIFY 7:1 formulations regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years.

There are no clinical data for AMPLIFY 7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly

No dose adjustment is considered necessary

Renal impairment

No dose adjustment is required in patients with creatinine clearance (CrCl) greater than 30 ml/min. In patients with creatinine clearance less than 30 ml/min, the use of AMPLIFY presentations with an amoxicillin to clavulanic acid ratio of 7:1 is not recommended, as no recommendations for dose adjustments are available.

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

METHOD OF ADMINISTRATION: AMPLIFY is for oral use.

AMPLIFY should be administered with a meal to minimise potential gastrointestinal intolerance.

4.3) CONTRAINDICATION:

Hypersensitivity to the active substances, to any of the penicillins or to any of the excipients listed in section 6.1.

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 (see section 4.8).

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 (see sections 4.3 and 4.8).

Serious and occasionally fatal hypersensitivity 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 must 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 AMPLIFY is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

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) (see section 4.8). This reaction requires AMPLIFY discontinuation and contraindicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

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 (see section 4.8).

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin and may range in severity from mild to life threatening (see section 4.8). 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, amoxicillin/clavulanic acid should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contraindicated 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 (see sections 4.5 and 4.8).

In patients with renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

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. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

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 AMPLIFY 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 (see sections 4.4 and 4.8).

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. Therefore, a change in the dose of mycophenolate mofetil should not normally be necessary in the absence of clinical evidence of graft dysfunction. However, close clinical monitoring should be performed during the combination and shortly after antibiotic treatment.

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 (see section 5.3). 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 breast-feeding might have to be discontinued. The possibility of sensitisation should be taken into account. 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 (see section 4.8).

4.8) UNDESIRABLE EFFECTS:

The most commonly reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

The ADRs derived from clinical studies and post-marketing surveillance with AMPLIFY , sorted by MedDRA System Organ Class are listed below.

The following terminologies have been used in order to classify the occurrence of undesirable effects.

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Infections and infestations	
Mucocutaneous candidosis	Common
Overgrowth of non-susceptible organisms	Not known
Blood and lymphatic system disorders	
Reversible leucopenia (including neutropenia)	Rare
Thrombocytopenia	Rare
Reversible agranulocytosis	Not known
Haemolytic anaemia	Not known
Prolongation of bleeding time and prothrombin time[1]	Not known
Immune system disorders[10]	

Angioneurotic oedema	Not known
Anaphylaxis	Not known
Serum sickness-like syndrome	Not known
Hypersensitivity vasculitis	Not known
Nervous system disorders	
Dizziness	Uncommon
Headache	Uncommon
Reversible hyperactivity	Not known
Convulsions[2]	Not known
Aeseptic meningitis	Not known
Gastrointestinal disorders	
Diarrhoea	Very common
Nausea[3]	Common
Vomiting	Common
Indigestion	Uncommon
Antibiotic-associated colitis[4]	Not known
Black hairy tongue	Not known
Hepatobiliary disorders	
Rises in AST and/or ALT[5]	Uncommon
Hepatitis[6]	Not known
Cholestatic jaundice[6]	Not known
Skin and subcutaneous tissue disorders[7]	
Skin rash	Uncommon
Pruritus	Uncommon
Urticaria	Uncommon
Erythema multiforme	Rare
Stevens-Johnson syndrome	Not known
Toxic epidermal necrolysis	Not known
Bullous exfoliative-dermatitis	Not known

Acute generalised exanthemous pustulosis (AGEP)[9]	Not known
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Not known
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

[1] See section 4.4

[2] See section 4.4

[3] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced by taking amoxicillin/clavulanic acid with a meal.

[4] Including pseudomembranous colitis and haemorrhagic colitis (see section 4.4)

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

[6] These events have been noted with other penicillins and cephalosporins (see section 4.4).

[7] If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued (see section 4.4).

[8] See section 4.9

[9] See section 4.4

[10] See sections 4.3 and 4.4

4.9) OVERDOSE:

Symptoms and signs of overdose

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4). Convulsions may occur in patients with impaired renal function or in those receiving high doses. Amoxicillin has been reported to precipitate in bladder catheters, predominantly after intravenous administration of large doses. A regular check of patency should be maintained (see section 4.4).

Treatment of intoxication

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

Amoxicillin/clavulanic acid can 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.

Pharmacokinetic/pharmacodynamic 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.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST).

Organism	Susceptibility Breakpoints (µg/ml)		
	Susceptible	Intermediate	Resistant
Haemophilus influenzae[1]	≤ 1	-	> 1
Moraxella catarrhalis[1]	≤ 1	-	> 1
Staphylococcus aureus [2]	≤ 2	-	> 2

Coagulase-negative staphylococci [2]	≤ 0.25		> 0.25
Enterococcus[1]	≤ 4	8	> 8
Streptococcus A, B, C, G[5]	≤ 0.25	-	> 0.25
Streptococcus pneumoniae[3]	≤ 0.5	1-2	> 2
Enterobacteriaceae[1,4]	-	-	> 8
Gram-negative Anaerobes[1]	≤ 4	8	> 8
Gram-positive Anaerobes[1]	≤ 4	8	> 8
Non-species related breakpoints[1]	≤ 2	4-8	> 8

[1] The reported values are for amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l.

[2] The reported values are oxacillin concentrations.

[3] Breakpoint values in the table are based on ampicillin breakpoints.

[4] The resistant breakpoint of R>8 mg/l ensures that all isolates with resistance mechanisms are reported resistant.

[5] Breakpoint values in the table are based on benzylpenicillin breakpoints.

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.

Commonly susceptible species

Aerobic Gram-positive micro-organisms

Enterococcus faecalis

Gardnerella vaginalis

Staphylococcus aureus (methicillin-susceptible)£

Coagulase-negative staphylococci (methicillin-susceptible)

Streptococcus agalactiae

Streptococcus pneumoniae[1]

Streptococcus pyogenes and other beta-haemolytic streptococci

Streptococcus viridans group

Aerobic Gram-negative micro-organisms

Capnocytophaga spp.

Eikenella corrodens

Haemophilus influenzae[2]

Moraxella catarrhalis

Pasteurella multocida

Anaerobic micro-organisms

Bacteroides fragilis

Fusobacterium nucleatum

Prevotella spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms

Enterococcus faecium $

Aerobic Gram-negative micro-organisms

Escherichia coli

Klebsiella oxytoca

Klebsiella pneumoniae

Proteus mirabilis

Proteus vulgaris

Inherently resistant organisms

Aerobic Gram-negative micro-organisms

Acinetobacter sp.

Citrobacter freundii

Enterobacter sp.

Legionella pneumophila

Morganella morganii

Providencia spp.

Pseudomonas sp.

Serratia sp.

Stenotrophomonas maltophilia

Other micro-organisms

Chlamydophila pneumoniae

Chlamydophila psittaci

Coxiella burnetti

Mycoplasma pneumoniae

$ Natural intermediate susceptibility in the absence of acquired mechanism of resistance.

£ All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid

[1]*Streptococcus pneumoniae* that are resistant to penicillin should not be treated with this presentation of amoxicillin/clavulanic acid (see sections 4.2 and 4.4).

[2] Strains with decreased susceptibility have been reported in some countries in the EU with a frequency higher than 10

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. 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 (875mg/125 mg tablets given twice 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 875/125 mg	875	11.64 ± 2.78	1.50 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA 875mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12
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 (see section 4.6).

Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (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 single AMPLIFY 250 mg/125 mg or 500 mg/125 mg 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 (see section 4.5).

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 (see section 4.2).

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.

6) PHARMACEUTICAL PARTICULARS:

6.1) LIST OF EXCIPIENTS

Each tablet contains:

Core Tablet :

1. Microcrystalline Cellulose
2. Sodium Starch Glycolate
3. Croscarmellose Sodium
4. Dibasic Calcium Phosphate (Anhydrous)
5. Magnesium Stearate

Coated Tablet :

6. Coating Premix White
7. Ethyl Cellulose
8. Diethyl phthalate
9. Isopropyl alcohol
10. Dichloromethane

6.2) INCOMPATIBILITIES:

Not Applicable

6.3) SHELF-LIFE :

2 Years

6.4) SPECIAL PRECAUTION FOR STORAGE:

Storage condition:

Store in a cool, dry place below 30 °C. Protect from light. Keep all Medicines out of reach of children.

6.5) NATURE AND CONTENTS OF CONTAINER:

2 Alu-Alu Blister of 7 Tablets packed in an aluminum pouch with silica gel, which is further packed in a Carton with leaflet.

6.5) SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING :

No special requirements. Any unused product or waste material should be disposed of in accordance with local requirements.

7) APPLICANT

SAI SAGAR PHARMA LIMITED

2, KAARA STREET, OFF OSOLO WAY,AJAO ESTATE, ISOLO, LAGOS

8) DATE OF PUBLICATION OR REVISION

Nigeria

Blister

Total Width : 256 mm

13 mm | 107 mm | 8 mm | 8 mm | 107 mm | 13 mm

AMPLIFY 1000 Tablets

POM

Amoxicillin & Clavulanate Potassium USP 1000 mg

Composition:
Each film coated tablet contains :
Amoxicillin USP (As Trihydrate)
equivalent to Amoxicillin 875mg
Clavulanate Potassium USP
equivalent to Clavulanic Acid 125mg
Excipients...q.s
Colour : Titanium Dioxide USP

Dosage : As directed by the physician.

Storage : Store below 30ºC, protected from light & moisture.

Keep all medicines out of sight & reach of children.

NAFDAC Reg. No. :

Sai

Marketed by
SAI SAGAR PHARMA LIMITED
No 2 Kaara Street, Off Osolo Way
Ajao Estate, Isolo, Lagos, Nigeria.

Manufactured in India by:-
SPARSH BIO-TECH PVT. LTD.
Lakhabavad, Jamnagar, Gujarat.
www.sparshbiotech.com
Mfg. Lic. No. : **G/1174**

AMPLIFY 1000 Tablets

POM

Amoxicillin & Clavulanate Potassium USP 1000 mg

Composition:
Each film coated tablet contains :
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equivalent to Amoxicillin 875mg
Clavulanate Potassium USP
equivalent to Clavulanic Acid 125mg
Excipients...q.s
Colour : Titanium Dioxide USP

Dosage : As directed by the physician.

Storage : Store below 30ºC, protected from light & moisture.

Keep all medicines out of sight & reach of children.

NAFDAC Reg. No. :

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Marketed by
SAI SAGAR PHARMA LIMITED
No 2 Kaara Street, Off Osolo Way
Ajao Estate, Isolo, Lagos, Nigeria.

Manufactured in India by:-
SPARSH BIO-TECH PVT. LTD.
Lakhabavad, Jamnagar, Gujarat.
www.sparshbiotech.com
Mfg. Lic. No. : **G/1174**

AMPLIFY 1000 Tablets

POM

Amoxicillin & Clavulanate Potassium USP 1000 mg

Composition:
Each film coated tablet contains :
Amoxicillin USP (As Trihydrate)
equivalent to Amoxicillin 875mg
Clavulanate Potassium USP
equivalent to Clavulanic Acid 125mg
Excipients...q.s
Colour : Titanium Dioxide USP

Dosage : As directed by the physician.

Storage : Store below 30ºC, protected from light & moisture.

Keep all medicines out of sight & reach of children.

NAFDAC Reg. No. :

Sai

Marketed by
SAI SAGAR PHARMA LIMITED
No 2 Kaara Street, Off Osolo Way
Ajao Estate, Isolo, Lagos, Nigeria.

Manufactured in India by:-
SPARSH BIO-TECH PVT. LTD.
Lakhabavad, Jamnagar, Gujarat.
www.sparshbiotech.com
Mfg. Lic. No. : **G/1174**

AMPLIFY 1000 Tablets

POM

Amoxicillin & Clavulanate Potassium USP 1000 mg

Composition:
Each film coated tablet contains :
Amoxicillin USP (As Trihydrate)
equivalent to Amoxicillin 875mg
Clavulanate Potassium USP
equivalent to Clavulanic Acid 125mg
Excipients...q.s
Colour : Titanium Dioxide USP

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Mfg. Lic. No. : **G/1174**

Foild Width : 256 mm
Bister Size : 123 x 85 mm
Repeat Length : 55 mm
Colour : Pantone 548 C, Black
Thickness : 0.04

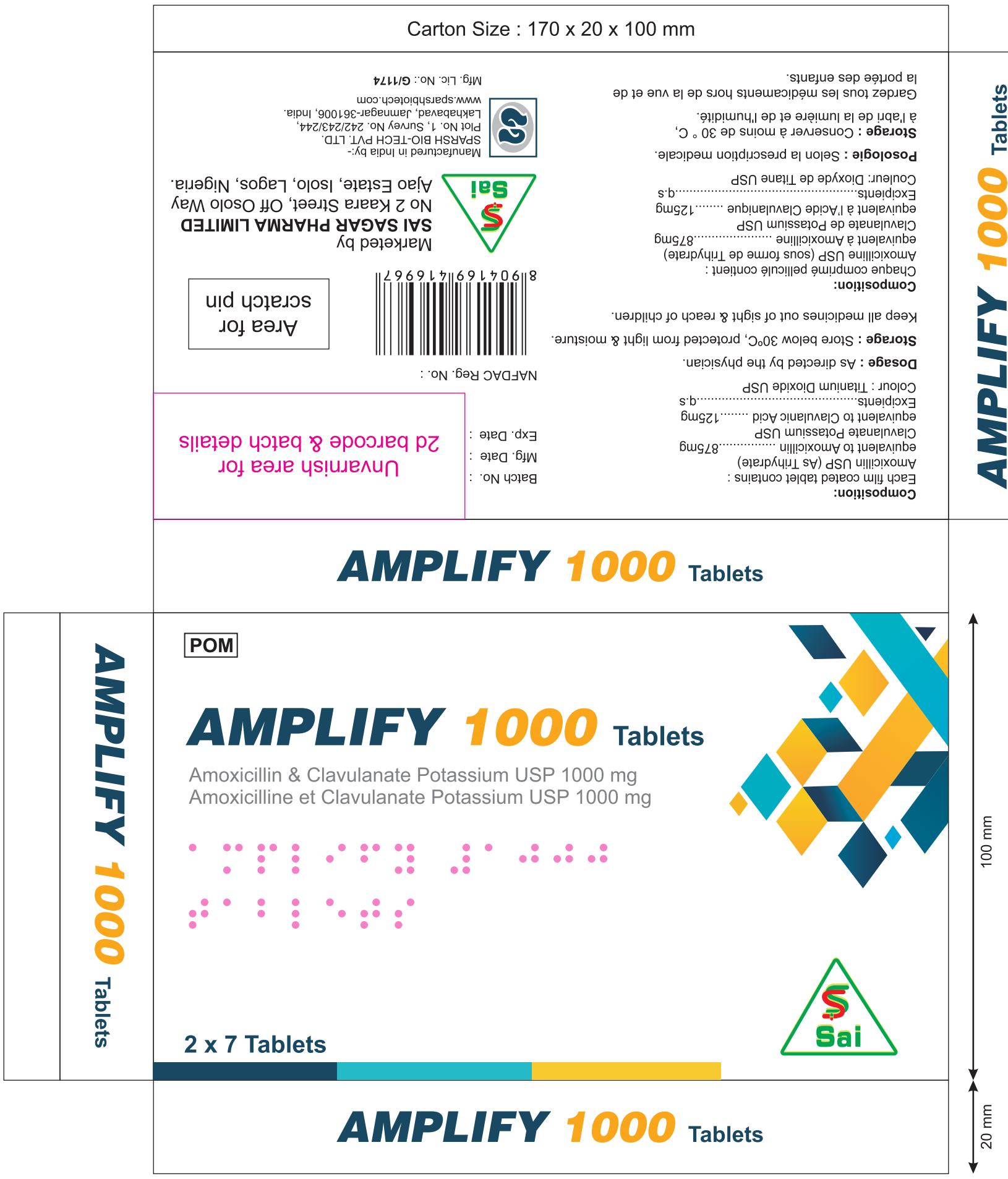
Colours	Product : AMPLIFY 1000 TABLETS	Artwork initiated by : Payal Vyas
Cyan Magenta Yellow Black Brand Name Braille **(4 Colour)**	Site : Sparsh Bio-Tech Pvt. Ltd. Size : L = 170 MM, W = 20 MM, H = 100 MM Color : 4 Colour Style : Carton (RTI) PACK : 2 x 10 Tablets (With Pouch) Buyer : Sai Sagar Pharma Ltd., Nigeria	Date :
Specifications: 320 gsm FBB Board + UV Brand Name Braille		**ERP Code :**

Shree Salespack Pvt. Ltd.

A M P L I F Y # 1 0 0 0 T A B L E T S

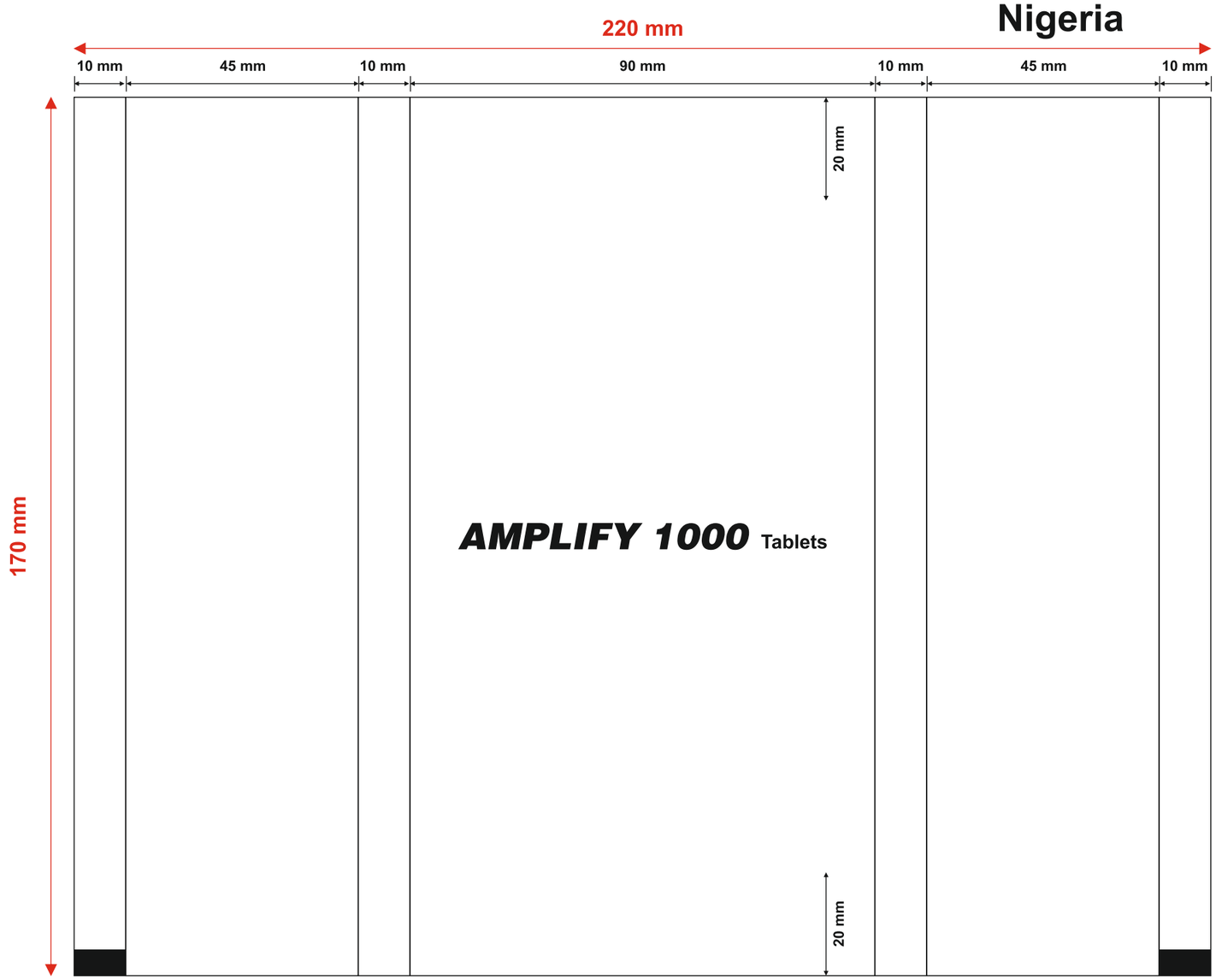
Nigeria

With Pouch



Check List	Check by QA Officer	Check by QC	Check by Packing / Purchase	Check by QA
Dimension:				
Colours:				
Brand Name/ Generic Name:				
Other Text Matter as per RA guideline:				
Mfg. Lic. / Code No.:				
ERP Code:				
Unvarnished area for Batch Detail/2D Barcode:				
Name:		Mr. Bhavesh Hingu	Mr. Haresh Maru	Mr. Ravi Sinojia
Sign :				

Nigeria



Photocel 10 x 5 mm

PET/FOIL/PE Based Three Ply Laminates Pouch.

Black

100 x 170 mm - Center Seal Pouch. Top & Bottom bothside Open