**Summary of Product Characteristics (SmPC)**

**ZIMILAT 625®**

**AMOXICILLIN 500MG / CLAVULANIC ACID 125MG**

This information is intended for use by health professional

## 1. Name of the medicinal product

Zimilat® 625mg caplet

## 2. Qualitative and quantitative composition

Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 125 mg of clavulanic acid.

For the full list of excipients, see section 6.1.

## 3. Pharmaceutical form

Film coated Caplet.

White to off white caplet inscribed with "Z" on one side and plain on the other sides.

## 4. Clinical particulars

### 4.1 Therapeutic indications.

Zimilat is 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

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 Zimilat® 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 Zimilat® (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 Zimilat® provides a total daily dose of 1500 mg amoxicillin/375 mg clavulanic acid, when administered as recommended below. For children < 40 kg, this formulation of Zimilat® provides a maximum daily dose of 2400 mg amoxicillin/600 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 Zimilat® 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).

Adults and children ≥ 40 kg

One 500 mg/125 mg dose taken three times a day.

Children < 40 kg

20 mg/5 mg/kg/day to 60 mg/15 mg/kg/day given in three divided doses.

Children may be treated with Zimilat® tablets, suspensions or pediatric dispersible tablets.

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

The table below presents the received dose (mg/kg body weight) in children weighing 25 kg to 40 kg upon administering a single 500/125 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) | 12.5 | 14.3 | 16.7 | 20.0 | 6.67 – 20 |
| Clavulanic acid [mg/kg body weight] per single dose (1 film-coated tablet) | 3.1 | 3.6 | 4.2 | 5.0 | 1.67 - 5 |

Children aged 6 years and below or weighing less than 25 kg should preferably be treated with Zimilat® suspension or pediatric dispersible tablets.

No clinical data are available on doses of Zimilat® 4:1 formulation higher than 40 mg/10 mg/kg per day in children under 2 years.

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 | 500 mg/125 mg twice daily |
| CrCl < 10 ml /min | 500 mg/125 mg once daily |
| Haemodialysis | 500 mg/125 mg every 24 hours, plus 500 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*

| | |
|---|---|
| CrCl: 10-30 ml/min | 15 mg/3.75 mg/kg twice daily (maximum 500 mg/125 mg twice daily). |
| CrCl < 10 ml /min | 15 mg/3.75 mg/kg as a single daily dose (maximum 500 mg/125 mg). |
| Haemodialysis | 15 mg/3.75 mg/kg per day once daily.<br>Prior to haemodialysis 15 mg/3.75 mg/kg. In order to restore circulating drug levels, 15 mg/3.75 mg per kg should be administered after haemodialysis. |

Hepatic impairment

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

Method of administration

Zimilat® is for oral use.

Zimilat® should be administered with a meal to minimize potential gastrointestinal intolerance.

Therapy can be started parenterally according the SPC of the IV formulation and continued with an oral preparation.

**4.3 Contraindications**

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 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 organism(s) then consideration should be given to switching from amoxicillin/clavulanic acid to amoxicillin in accordance with official guidance.

This presentation of Zimilat® 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 generalized erythema associated with pustula may be a symptom of acute generalized exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires Zimilat® 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 Zimilat® 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.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

## 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 normalized ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalized 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 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 (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 Zimilat® 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

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product

**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<br>*Enterococcus faecalis*<br>*Gardnerella vaginalis*<br>*Staphylococcus aureus* (methicillin-susceptible)**<br>Coagulase-negative staphylococci (methicillin-susceptible)<br>*Streptococcus agalactiae*<br>*Streptococcus pneumoniae*[1]<br>*Streptococcus pyogenes* and other beta-haemolytic streptococci<br>*Streptococcus viridans* group<br>Aerobic Gram-negative micro-organisms<br>*Capnocytophaga* spp.<br>*Eikenella corrodens*<br>*Haemophilus influenzae*[2]<br>*Moraxella catarrhalis*<br>*Pasteurella multocida*<br>Anaerobic micro-organisms<br>*Bacteroides fragilis*<br>*Fusobacterium nucleatum*<br>*Prevotella* spp. |
| Species for which acquired resistance may be a problem |
| Aerobic Gram-positive micro-organisms<br>*Enterococcus faecium* *<br>Aerobic Gram-negative micro-organisms<br>*Escherichia coli*<br>*Klebsiella oxytoca*<br>*Klebsiella pneumoniae*<br>*Proteus mirabilis*<br>*Proteus vulgaris* |
| Inherently resistant organisms |
| Aerobic Gram-negative micro-organisms<br>*Acinetobacter* sp.<br>*Citrobacter freundii* |

| |
|---|
| *Enterobacter* sp.<br>*Legionella pneumophila*<br>*Morganella morganii*<br>*Providencia* spp.<br>*Pseudomonas* sp.<br>*Serratia* sp.<br>*Stenotrophomonas maltophilia*<br>Other micro-organisms<br>*Chlamydophila pneumoniae*<br>*Chlamydophila psittaci*<br>*Coxiella burnetti*<br>*Mycoplasma pneumoniae* |
| * Natural intermediate susceptibility in the absence of acquired mechanism of resistance.<br>** All methicillin-resistant staphylococci are resistant to amoxicillin/clavulanic acid<br>[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).<br>[2] Strains with decreased susceptibility have been reported in some countries 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 (500 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 500/125 mg | 500 | 7.19 ± 2.26 | 1.5 (1.0-2.5) | 53.5 ± 8.87 | 1.15 ± 0.20 |
| Clavulanic acid | | | | | |
| AMX/CA 500 mg/125 mg | 125 | 2.40 ± 0.83 | 1.5 (1.0-2.0) | 15.72 ± 3.86 | 0.98 ± 0.12 |
| AMX – amoxicillin, CA – clavulanic acid<br>* 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 Zimilat® 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

***Tablet core*:**

Sodium starch glycolate

Cross carmelose sodium

Povidone (PVP k-30)

Colloidal silicon dioxide

Magnesium stearate

Purified Talcum powder

***Seal & Film Tablet coating*:**

Hypromellose E5 Talc

Titanium dioxide (E171)

PEG

Ethyl cellulose

Diethyl phthalate

Methylene dichloride

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

2 years

### 6.4 Special precautions for storage

Store in the original package to protect from moisture.

Do not store above 30°C.

**6.5 Nature and contents of container**

Caplets are packed in Aluminum/Aluminum (Alu-Alu) blisters of 7 caplets per blister. 2 of such blisters are packed in an inner packet accompanied by a patient information leaflet.

**6.6 Special precautions for disposal and other handling**

Any unused product or waste material should be disposed of in accordance with local requirements.

**7. Marketing authorization holder**/Applicant/Manufacturer:

**NEMEL Pharmaceuticals Limited**

Plot 35 Emene Industrial Layout

Enugu, Nigeria.

**8. Marketing authorization number(s)**

B4-1592.

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

3rd December, 2015.

**10. Date of revision of the text**

21st January, 2020.