SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CLANEKSI® Forte

Amoxicillin and Clavulanate Potassium for Oral Suspension Dry Syrup

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

When dispersed with boiled and cooled water, each 5 ml contains: Amoxicillin Trihydrate equivalent to 250 mg of Amoxicillin.
Clavulanate Potassium equivalent to 62.5 mg of Clavulanic Acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Dry Syrup
White homogeneous powder with tutti frutti odor.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

CLANEKSI® Forte is indicated for the treatment of the following infections:

- Upper respiratory tract infections e.g tonsillitis, sinusitis, otitis media.
- Lower respiratory tract infections e.g acute and chronic bronchitis, lobar and bronchopneumonia.
- Genito-urinary tract infections e.g abscesses, cellulitis, boils.
- Bone and joint infections e.g osteomyelitis.
- Dental infections e.g dentoalveolar abscess.
- Other infections e.g septic abortion, puerperal sepsis, intraabdominal sepsis.

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

4.2 Posology And Method of Administration

To minimize potential gastrointestinal intolerance, administer **CLANEKSI® Forte** at the start of a meal.
For the treatment of infection:
Children : The usual dose is 25 mg/kg of body weight daily in divided doses every 8 hours.
< 1 year : 2 ml of dry syrup 156.25 mg, 3 times daily. 1-6 years (10-18 kg): 5 ml of dry syrup 156.25 mg, 3 times daily
> 6 years : 5 ml of dry syrup 312.5 mg, 3 times daily
The duration of **CLANEKSI® Forte** therapy should be determined by the response of the patient. Some infections require longer periods of treatment. Treatment should not be extended beyond 14 days without review.

Direction for Reconstitution:
Pour boiled and cooled water until slightly below mark. Close bottle tightly. Hold bottle upside-down, shake and allow to stand for 5 minutes to ensure full dispersion. Add sufficient boiled and cooled water up to mark (60 ml) and shake well. After reconstitution, the suspension must be used within 7 days. Store in a refrigerator.

Dosage in patients with impaired renal function:
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.
Patients with moderate impairment (Creatinine clearance 10 -30 ml/min) adjust dose 375 mg or 625 mg every 12 hours.

Patients with severe impairment (Creatinin clearance < 10 ml/min) not more than 375 mg every 12 hours.

Dosage in elderly patients (> 65 years of age)
Do dosage adjustment is necessary in elderly patients

Dosage in patients with impaired hepatic function
Dose with caution and monitor hepatic function at regular intervals.

Method of Administration
CLANEKSI® Forte Dry Syrup is for oral use after reconstituted with pour boiled and cooled water.

4.3 Contraindications
- Hypersensitivity to penicillin
- In neonatal whose mother is hypersensitive to penicillin sir its derivative
- History of cholestatic jaundice (hepatic dysfunction)

4.4 Special warnings and precautions for use
Before inisiating therapy with **CLANEKSI**, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.
Serious and occasionally fatal hypersensitivity reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of amoxicillin/clavulanic acid theraphy must be discontinued and appropriate alternative therapy instituted.
In the case that an infection is proven to be due to an amoxicilline-susceptible organisme(s) then consideration should be given to switching from amoxicillin/clavulanic acid. This presentation should not be used to treat penicillin-resistant S.*pneumoniae*.

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

High dose or prolonged administration may induce superinfection (caused by Enterobacter, Pseudomonas, S.*aureus*, candida), Primarily in gastrointestinal tract.

CLANEKSI® Forte 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.

CLANEKSI® Forte is not recommended to pregnant and nursing mother except on medical recommendation

4.5 Interactionwith Other Medicinal Products and Other Forms of Interactions

CLANEKSI® Forte May reduce the efficacy of oral contraceptives.
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

4.6 Pregnancy and Lactation

4.6.1. Fertility

Animal studies do not indicate direct or indirect harmful effects with respect to male and female fertility**.**

4.6.2. 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 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 **CLANEKSI® Forte** may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.

4.6.3. Lactation

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 sensitization.

should be taken into account. **CLANEKSI® Forte** should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.7 Effect on Ability to Drive and Use Machine

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

- Diarrhea, nausea, vomiting, indigestion, pseudomembranous colitis and candidiasis
- A moderate rise in AST and/or ALT has been notes in patients with semisynthetic penicillins.
- Hepatitis and cholestatic jaundice, may be severe and adult or elderly patients and slightly more frequently in males. Signs and symptoms may occur during treatment but are more frequently reported after cessation of therapy with a delay of up to 6 weeks. The hepatic events are usually reversible.
- Urticarial and erythematous rashes.
- Erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis and exfoliative dermatitis. Treatment should be discontinued if these reactions occur.
- Angioedema and anaphylaxis.
- Interstitial nephritis
- Transient leucopenia, thrombocytopenia and haemolytic anemia.

Reporting of suspected adverse reactions

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via Pharmacy and the Poisons Board, Pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 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. 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.
Treatment of intoxication Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance. **CLANEKSI® Forte** can be removed from the circulation by haemodialysis

5. PHARMACOLOGICAL PROPERTIES

5.1 Phamacodynamic

properties Mechanisms of Action:

Amoxicillin is a semisynthetic antibiotic derivated from penicillin, with a broad spectrum of bactericidal acitivity against many Gram-positive and Gram-negative microorganism, the bactericidal effect of Amoxicillin inhibits the bactericidal cell wall is weaked, the plasma cell swells and then ruptures.

Clavulanic acid is a β-lactamase enzyme inhibitor produced by certain bacteria. The mechanisms of action of Clavulanic acid are:

First: As a competitive inhibitor, structurally related to the penicillins, then Clavulanic acid replaces the active sites of β-lactamase enzyme structure without the chemical reactions.

Second: The carbonil group of β-lactamase of Clavulanic acid transform penicillinase enzyme to acyl enzyme. The acyl enzyme form is not active against penicillin.

Pharmacokinetic/pharmacodynamics 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 **CLANEKSI® Forte** 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.

Susceptibility:

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.

1 The reported values are oxacillin concentrations.

2 Breakpoint values in the table are based on ampicillin breakpoints.

3 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
aemophilus
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
pneumonia
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
pneumonia

$ 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 **CLANEKSI**.
[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
CLANEKSI® Forte is 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. Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similar to those produced by the oral administration of equivalent doses of amoxicillin or clavulanic acid alone.

Distribution

About 25% of total plasma clavulanic acid and 18% of total plasma amoxicillin is bound to protein. The apparent volume of distribution is around 0.3-0.4 l/kg for amoxicillin and around 0.2 l/kg for clavulanic acid.
Following intravenous administration, both amoxicillin and clavulanic acid have been found in gall bladder, abdominal tissue, skin, fat, muscle tissues, synovial and peritoneal fluids, bile and pus. Amoxicillin does not adequately distribute into the cerebrospinal fluid. From animal studies there is no evidence for significant tissue retention of drug-derived material for either component. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanic acid can also be detected in breast milk. Both amoxicillin and clavulanic acid have been shown to cross the placental barrier.
Biotransformation
Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to up to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine and faeces and as carbon dioxide in expired air.

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

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

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

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.

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

6. PHARMACEUTICAL PARTICULARS
6.1 List of Excipients
Silicon Dioxide
Colloidal Xantham
Gum
Carboxymethylcellulose
Sodium Mannitol
Succinic Acid
Saccharine
Sodium Tutti
Frutti Dry Flavor

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
Dry powder: 24 months
Reconstituted suspension: 7 days

6.4 Special Precaution for Storage
Store the dry powder in the original container. Store dry powder below 30°C in dry place, away from light.
For reconstituted **CLANEKSI® Forte** store in a refrigerator, must be used within 7 days.

6.5 Nature and Contents of Containers
Clear glass bottle containing powder for reconstitution to 60 ml. This may be supplied with a measuring spoon or cup.

6.6 Special Precautions for Disposal and other Handling
Check cap seal is intact before using. Shake bottle to loosen powder. Add volume of water (as indicated below). Invert and shake well.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

Marketing Authorization Holder

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H2010/19988/745

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