Vadis® Amoxicillin Trihydrate + Potassium Clavulanate

Module 1- Administrative information and prescribing information

1.3 Product Information

1.3.1 Summary of Product Characteristics (SmPC)

Enclosed

Summary Product Characteristics (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

Vadis® Amoxicillin Trihydrate + Potassium Clavulanate
(Amoxicillin and Potassium Clavulanate Tablets BP 625 mg)

Strength

Each film coated tablet contains:
Amoxicillin Trihydrate BP
Equivalent to Amoxicillin……..500 mg
Potassium Clavulanate Diluted BP
Equivalent to Clavulanic Acid ……125 mg
Excipients……Q.S.
Colour: Titanium Dioxide

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Description: White colour, capsule shape, biconvex, film coated tablet plain on both side.

Sr. No	Ingredients	Spec	Qty./tab (mg)	(%) Over-ages	Quantity /tab with Overages (mg)	Category
Dry Mixing						
1.	Amoxicillin Trihydrate	BP	573.90 ≈ 500.00	-	573.90	API
2.	Potassium Claulanate	BP	148.91 ≈ 125.00	-	148.91	API
3.	Microcrystalline Cellulose	BP	50.00	-	50.00	Diluent
Lubrication						
4.	Cross Carmelose Sodium.	BP	33.00	-	33.00	Lubricant
5.	Colloidal Silicon Dioxide	BP	35.00	-	35.00	Lubricant
6.	Purified Talc	BP	22.19	-	22.19	Glidant
7.	Sodium Starch Glycolate	BP	20.00	-	20.00	Disintegrant.
8.	Magnesium Stearate	BP	20.00	-	20.00	Lubricant
Total Weight of Uncoated Tablets			**903.00**		**903.00**	
Coating						
9.	Colour Titanium Di Oxide	In-House	27.00	-	27.00	Coating agent
10.	Isopropyl Alcohol	BP	210.00	-	210.00	Vehicle
11.	Methylene Chloride	BP	286.00	-	286.00	Vehicle
Total Weight of Coated Tablets			**930.00**		**930.00**	

BP: British Pharmacopeia

1) ** Quantity evaporates during of manufacturing, required quantity to be used.

3. PHARMACEUTICAL FORM

Film Coated Tablets

White to off white Colour, oblong shape, Biconvex, film coated tablet with one side break line and other side plain

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Amoxicillin and Potassium Clavulanate Tablets is indicated for the treatment of the following infections in adults and children:

- 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 **Amoxicillin and Potassium Clavulanate Tablets** that is selected to treat an individual infection should take into account:

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

For adults and children ≥ 40 kg, this formulation of **Amoxicillin and Potassium Clavulanate Tablets** 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 **Amoxicillin and Potassium Clavulanate Tablets** 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 **Amoxicillin and Potassium Clavulanate Tablets** is selected in order to avoid administration of unnecessarily high daily doses of clavulanic acid.

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.

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 A **Amoxicillin and Potassium Clavulanate Tablets**, suspensions or paediatric sachets.

As the tablets cannot be divided, children weighing less than 25 kg must not be treated with **Amoxicillin and Potassium Clavulanate 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]
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 **Amoxicillin and Potassium Clavulanate Tablets** suspension or paediatric sachets.

No clinical data are available on doses of **Amoxicillin and Potassium Clavulanate Tablets** 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. 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.
Method of administration
Amoxicillin and Potassium Clavulanate Tablets is for oral use.
Administer at the start of a meal to minimise potential gastrointestinal intolerance and optimise absorption of amoxicillin/clavulanic acid.
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.
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.

4.4 Special warnings and precautions for use

Before initiating therapy with amoxicillin/clavulanic acid, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta-lactam agents.
Serious and occasionally fatal hypersensitivity (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 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 **Amoxicillin and Potassium Clavulanate Tablets** 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.
Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since the occurrence of a morbilliform rash has been associated with this condition following the use of amoxicillin.
Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions.
Prolonged use may occasionally result in overgrowth of non-susceptible organisms.

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP).

This reaction requires **Amoxicillin and Potassium Clavulanate Tablets** discontinuation and contra-indicates any subsequent administration of amoxicillin.

Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment.

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

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

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

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

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

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

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 **Amoxicillin and Potassium Clavulanate Tablets** 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 Paediatric population

Not Applicable

4.6 Interaction with other medicinal products and other forms of interaction

Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, in the literature there are cases of increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.
Methotrexate
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 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.

4.7 Additional information on special populations

Non known

4.8 Fertility, pregnancy and lactation

Pregnancy
Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin/clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates. Use should be avoided during pregnancy, unless considered essential by the physician.
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. Amoxicillin/clavulanic acid should only be used during breast-feeding after benefit/risk assessment by the physician in charge.

4.9 Effects on ability to drive and use machines

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

4.10 Undesirable effects

Common : Mucocutaneous candidosis, Diarrhoea, Nausea, Vomiting

Uncommon : Dizziness, Headache, Indigestion, Rises in AST and/or ALT, Skin rash, Pruritus, Urticaria

Rare : Reversible leucopenia (including neutropenia), Thrombocytopenia, Erythema multiforme

4.11 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.

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.

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.

Mode 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.

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. Absorption of amoxicillin/clavulanic acid is optimised when taken at the start of a meal. 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 * 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.

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 **Amoxicillin and Potassium Clavulanate Tablets** 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.

5.3 Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic potential.

4:1 ratio formulation of Amoxicillin:Clavulanate was non-mutagenic in the Ames bacterial mutation assay, and the yeast gene conversion assay. Amoxicillin:Clavulanate was weakly positive in the mouse lymphoma assay, but the trend toward increased mutation frequencies in this assay occurred at doses that were also associated with decreased cell survival. Amoxicillin:Clavulanate was negative in the mouse micronucleus test, and in the dominant lethal assay in mice. Potassium clavulanate alone was tested in the Ames bacterial mutation assay and in the mouse micronucleus test, and was negative in each of these assays.

2:1 ratio formulation of Amoxicillin: Clavulanate at oral doses of up to 1,200 mg/kg/day was found to have no effect on fertility and reproductive performance in rats. Based on body surface area, this dose of amoxicillin is approximately 4 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, the dose multiple is approximately 9 times higher than the maximum recommended adult human oral dose (125 mg every 8 hours), also based on body surface area.

Use In Specific Populations

Pregnancy

Teratogenic Effects

Pregnancy Category B. Reproduction studies performed in pregnant rats and mice given 2:1 ratio formulation of Amoxicillin: Clavulanate at oral doses up to 1200 mg/kg/day revealed

no evidence of harm to the fetus due to Amoxicillin: Clavulanate. The amoxicillin doses in rats and mice (based on body surface area) were approximately 4 and 2 times the maximum recommended adult human oral dose (875 mg every 12 hours). For clavulanate, these dose multiples were approximately 9 and 4 times the maximum recommended adult human oral dose (125 mg every 8 hours). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Labor and Delivery

Oral ampicillin-class antibiotics are poorly absorbed during labor. It is not known whether use of amoxicillin/clavulanate potassium in humans during labor or delivery has immediate or delayed adverse effects on the fetus, prolongs the duration of labor, or increases the likelihood of the necessity for an obstetrical intervention.

Nursing Mothers

Amoxicillin has been shown to be excreted in human milk. Amoxicillin/clavulanate potassium use by nursing mothers may lead to sensitization of infants. Caution should be exercised when amoxicillin/clavulanate potassium is administered to a nursing woman..

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Microcrystalline Cellulose	BP
Cross Carmelose Sodium.	BP
Colloidal Silicon Dioxide	BP
Purified Talc	BP
Sodium Starch Glycolate	BP
Magnesium Stearate	BP
Colour Titanium Di Oxide	In-House
Isopropyl Alcohol	BP
Methaline Dichloride	BP

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30˚C. Protect from light.

6.5 Nature and contents of container

1 X 6 Tablets in Alu-Alu Pack

6.6 Special precautions for disposal and other handling

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN.

7. MARKETING AUTHORIZATION HOLDER AND MANUFACTURING SITE ADDRESSES

MANUFACTURING SITE ADDRESSES
First Vadis Pharmaceutical Industries Limited
Plot IN/2 Phase 2 Extension, Emene
Industrial Layout Enugu State

8. MARKETING AUTHORIZATION NUMBER

Not applicable

9. DATE OF FIRST <REGISTRATION> / RENEWAL OF THE <REGISTRATION>

Not applicable

10. DATE OF REVISION OF THE TEXT