SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OXYNIC 312.5 (Amoxicillin and Potassium Clavulanate Oral Suspension BP)

2.QUALITATIVE AND QUANTITA TIVE COMPOSITION

After reconstitution each 5ml contains

Amoxicillin Trihydrate BP

Eq. to Amoxicillin .....250 mg

Diluted Potassium Clavulanate BP

Eq. to Clavulanic acid……..62.5 mg

Exipients.....Q.S.

3. PHARMACEUTICAL FORM

Oral suspension

White to off white crystalline powder which become white suspension on addition of water.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of bacterial infections induced by gram negative and gram-positive amoxicillin-resistant microorganisms whose resistance is caused by β-lactamases which however are sensitive to the combination of amoxicillin and clavulanic acid.

Co-amoxiclav Potassium Oral Suspension is suitable for treatment of the following indications when known or likely to be due to susceptible organisms:

Infections of the upper respiratory tract (including ear-nose-throat) in particular sinusitis, otitis media, recurrent tonsillitis.

Infections of the lower respiratory tract, in particular acute exacerbations of chronic bronchitis and bronchopneumonia.

Genital and urinary tract infections.

Infections of the skin and soft tissues

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

4.2 Posology and method of administration

Adults and children weighing 40 kg or over

• This suspension is not usually recommended for adults and children weighing 40 kg and over.

Ask your doctor or pharmacist for advice.

Children weighing less than 40 kg

All doses are worked out depending on the child's bodyweight in kilograms.
Your doctor will advise you how much Co-amoxiclav Oral Suspension you should give to your baby or child.

You may be provided with a plastic measuring spoon. You should use this to give the correct dose to your baby or child.

Usual dose – 20 mg/5 mg to 60 mg/15 mg for each kilogram of body weight a day, given in three divided doses.
Patients with kidney and liver problems
If your child has kidney problems the dose might be lowered. A different strength or a different medicine may be chosen by your doctor.
If your child has liver problems they may have more frequent blood tests to see how their liver is working.
How to give Co-amoxiclav Oral Suspension
• Always shake the bottle well before each dose
• The measuring spoon provided is marked to show doses of
1.25 ml, 2.5 ml and 5 ml. If you are using the measuring spoon, take care to ensure it is filled to the correct dosage marking.
- To measure 1.25 ml of suspension, carefully tilt the spoon and fill up to the dosing line marked 1.25 ml.
- To measure 2.5 ml of suspension, keep the spoon level and fill up to the dosing line marked 2.5 ml.
- To measure 5 ml of suspension, keep the spoon level and fill up to the brim.
Ask your doctor or pharmacist if you are unsure.
• Give at the start of a meal or slightly before
• Space the doses evenly during the day, at least 4 hours apart. Do not take 2 doses in 1 hour.
• Do not give your child Co-amoxiclav Oral Suspension for more than 2 weeks. If your child still feels unwell they should go back to see the doctor.

4.3 Contraindications

Hypersensitivity to amoxicillin, clavulanic acid, β-lactams (e.g. penicillins, cephalosporins) owing to the danger of anaphylactic shock, or to any of the excipients.
Co-amoxiclav Potassium Oral Suspension should not be used in patients in whom hepatic functional impairment has occurred during previous treatment with amoxicillin/clavulanic acid.
Amoxicillin/clavulanic acid must not be used in patients with severe hepatic functional impairment. Patients with infectious mononucleosis (glandular fever) and patients with lymphatic leukaemia have a higher risk of developing exanthema if given amoxicillin/clavulanic acid. Consequently amoxicillin/clavulanic acid should not be administered to patients with these conditions.

Phenylketonuria since the product contains aspartame.

4.4 Special warnings and precautions for use

Before initiating therapy with OXYNIC 312.5 , careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens.

Serious and occasionally fatal hypersensitivity (anaphylactoid) reactions have been reported in patients on penicillin therapy. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity.

OXYNIC 312.5 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.

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. 5 Pseudomembranous colitis has been reported with the use of antibiotics and may range in severity from mild to life-threatening. Therefore, it is important to consider its diagnosis in patients who develop diarrhoea during or after antibiotic use. If prolonged or significant diarrhoea occurs or the patient experiences abdominal cramps, treatment should be discontinued immediately and the patient investigated further.

Abnormal prolongation of prothrombin time (increased INR) has been reported rarely in patients receiving OXYNIC 312.5 and oral anticoagulants. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently. Adjustments in the dose of oral anticoagulants may be necessary to maintain the desired level of anticoagulation.

Changes in liver function tests have been observed in some patients receiving OXYNIC 312.5 . The clinical significance of these changes is uncertain but OXYNIC 312.5 should be used with caution in patients with evidence of hepatic dysfunction.

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

In patients with renal impairment OXYNIC 312.5 suspension is not recommended.

In patients with reduced urine output, crystalluria has been observed very rarely, predominantly with parenteral therapy. During the administration of high doses of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillin crystalluria.

4.5 Interaction with other medicinal products and other forms of interaction

<u>Oral anticoagulants</u>

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 (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.

Breast feeding

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

Adverse effects on the ability to drive or operate machinery have not been observed.

4.8 Undesirable effects

Approximately 5% of patients can be expected to experience adverse reactions. Gastrointestinal disorders with loose stools, nausea and vomiting occur more frequently at higher doses and have been reported more frequently compared to treatment with amoxicillin alone.

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)

Infections and infestations
Uncommon
Prolonged and repeated use of the preparation can result in superinfections and colonisation with resistant organisms or yeasts.

<u>Blood and the lymphatic system disorders</u>
Rare
Thrombocystosis, haemolytic anaemia
Very rare
Changes in blood count in form of leucopenia, agranulocytosis, granulocytopenia, thrombocytopenia, pancytopenia, anaemia or myelosuppression and prolongation of the bleeding and prothrombin time have been observed in isolated cases. These manifestations are reversible after discontinuation of therapy.
<u>Immune system disorders</u>
Rare
Typical type I allergic reactions (such as urticaria, purpura), angio-oedema and anaphylaxis can occur less frequently. Erythema multiforme, Lyell syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised erythematous pustulosis, bullous exfoliative dermatitis, serume sickness and vasculitis associated with hypersensitivity rarely occur.

Drug fever.

Psychiatric disorders

Very rare

Hyperactivity, anxiety, sleeplessness, mental confusion and aggression.

Nervous system disorders

Rare

Dizziness, headache and convulsions are rare. Convulsions may occur with impaired renal function or in those receiving high doses.

Gastrointestinal disorders

Common

Gastro-intestinal disturbances such as nausea, vomiting and diarrhoea and pruritis ani have been observed. These side effects are generally of a mild and transitory nature.

Rare

Pseudomembranous colitis, haemorrhagic colitis, mucocutaneous candidiasis, superficial tooth discoloration.

Very rare

Development of a black tongue.

A single study in women with premature rupture of the amnion reported that prophylactic treatment with amoxicillin/clavulanic acid can be associated with an increased risk of necrotising enterocolitis in neonates

Hepato-biliary disorders

Rare

In rare cases a moderate rise in AST and/or ALT values has been reported.

Very rare

Hepatitis and cholestatic jaundice have been reported rarely. Hepatic events occur predominantly in males and elderly patients, particularly those over 60 years of age. The risk of these events occurring increases with treatment for more than 14 days. These side effects are very rarely reported in children. Signs and symptoms usually occur during or shortly after treatment but in some cases may not become apparent until some weeks after treatment has ceased. Hepatic events are usually transient. However they may be severe and in very rare cases a fatal outcome has been reported. These have mostly occurred in patients with a serious underlying disease, or patients taking potentially hepatotoxic agents in addition to amoxicillin/clavulanic acid.

Skin and subcutaneous tissue disorders

Common

Allergic skin reactions occur significantly more often than with other penicillins and generally are maculopapular in nature. In some cases ‘fifth day rash’ (a morbilliform exanthema) is reported. This is dependent on the size of the dose and the patient’s condition.

Renal and urinary disorders

Very rare

Interstitial nephritis has occurred on a single occasion. Crystalluria has been reported.

Reproductive system and breast disorders

Uncommon

Vaginal itching and discharge.

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;

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.
Eikenellacorrodens
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* *Klebsiellaoxytoca* *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*

Coxiellaburnetti *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 . [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 (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	C_{max}	T_{max} *	AUC $_{(0-24h)}$	T 1/2
	(mg)	(µg/ml)	(h)	(µg/ml)	(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	125	2.40	1.5	15.72	0.98

500 mg/125 mg		± 0.83	(1.0-2.0)	± 3.86	± 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.

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.

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 OXYNIC 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 .

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

Not applicable.

6. Pharmaceutical particulars

6.1 List of excipients

Sr. No.	Excipients	Specification
1	Colloidal anhydrous silica	BP
2	Hypromellose	
3	Xanthan Gum	BP
4	Aspartame	BP
5	Citric acid anhydrous	BP
6	Sodium benzoate	BP
7	Silicon Dioxide	USP
8	Essence dry Mango	IH

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30^0C. Protect from light & moisture. Keep out of reach of children.

6.5 Nature and contents of container

70 ml HDPE bottle.

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing authorization holder

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