1.10 Summary of Product Characteristics

OXYNIC 1000 **GB PHARMA LIMITED**
Amoxicillin and Potassium Clavulanate Tablets BP

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1. NAME OF THE MEDICINAL PRODUCT

OXYNIC 1000 (Amoxicillin and Potassium Clavulanate Tablets BP)

2.QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tabletcontains

Amoxicillin Trihydrate BP

Eq. to Amoxicillin .....875 mg

Diluted Potassium Clavulanate BP

Eq. to Clavulanic acid……..125 mg

Exipients.....Q.S.

Colours: Approved colours used

3. PHARMACEUTICAL FORM

Film coated tablet

White colored,biconvex capsule shaped film coated tablet with both side plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxynicis 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.

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 Oxynicthat 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 Oxynic(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 Oxynicprovides a total daily dose of 1750 mg amoxicillin/ 250 mg clavulanic acid with twice daily dosing and 2625 mg amoxicillin/375 mg clavulanic acid with three times daily dosing, when administered as recommended below.

For children < 40 kg, this formulation of Oxynicprovides a maximum daily dose of 1000-2800 mg amoxicillin/143-400 mg clavulanic acid, when administered as recommended below. If it is considered that a higher daily dose of amoxicillin is required, it is recommended that another preparation of Oxynicis 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

Recommended doses:

• standard dose: (for all indications) 875 mg/125 mg two times a day;

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

Children < 40 kg

Children may be treated with Oxynictablets, suspensions or paediatric sachets.

Recommended doses:

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

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

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

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

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

Children weighing less than 25 kg should preferably be treated with Oxynicsuspension or paediatric sachets.
No clinical data are available for Oxynic7:1 formulations regarding doses higher than 45 mg/6.4 mg per kg per day in children under 2 years.
There are no clinical data for Oxynic7:1 formulations for patients under 2 months of age. Dosing recommendations in this population therefore cannot be made.

Elderly
No dose adjustment is considered necessary.

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

Hepatic impairment
Dose with caution and monitor hepatic function at regular intervals .
Method of administration
Oxynicis for oral use.Oxynicshould be administered with a meal to minimise potential gastrointestinal intolerance.

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-lactamagents (see sections 4.3 and 4.8).

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 historyof 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 Oxynicis not suitable for use when there is a high risk that the presumptive
pathogens have resistance to beta-lactam agents that is not mediated by beta-lactamases susceptibleto 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 (see4.8).

Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected since theoccurrence of a morbilliform rash has been associated with this condition following the use ofamoxicillin.

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 pustulamay be a symptom of acute generalised exanthemous pustulosis (AGEP) (see Section 4.8). Thisreaction requires Oxynicdiscontinuation and contra-indicates any subsequent administration ofamoxicillin.

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 beassociated with prolonged treatment. These events have been very rarely reported in children. In allpopulations, signs and symptoms usually occur during or shortly after treatment but in some casesmay 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 takingconcomitant 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 isimportant to consider this diagnosis in patients who present with diarrhoea during or subsequent tothe administration of any antibiotics. Should antibiotic-associated colitis occur, Oxynicshouldimmediately be discontinued, a physician be consulted and an appropriate therapy initiated. Antiperistalticdrugs are contra-indicated in this situation.

Periodic assessment of organ system functions, including renal, hepatic and haematopoietic functionis advisable during prolonged therapy.
Prolongation of prothrombin time has been reported rarely in patients receivingamoxicillin/clavulanic acid. Appropriate monitoring should be undertaken when anticoagulants areprescribed concomitantly. Adjustments in the dose of oral anticoagulants may be necessary tomaintain the desired level of anticoagulation (see section 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 withparenteral therapy. During the administration of high doses of amoxicillin, it is advisable tomaintain adequate fluid intake and urinary output in order to reduce the possibility of amoxicillincrystalluria. In patients with bladder catheters, a regular check of patency should be maintained (seesection 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 nonenzymaticmethods.
The presence of clavulanic acid in Oxynicmay 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 AspergillusEIA test in patients receiving amoxicillin/clavulanic acid who were subsequently found to be free ofAspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses withBio-Rad Laboratories Platelia Aspergillus EIA test have been reported. Therefore, positive testresults in patients receiving amoxicillin/clavulanic acid should be interpreted cautiously andconfirmed by other diagnostic methods.

4.5 Interaction with other medicinal products and other forms of interaction
Oral anticoagulants
Oral anticoagulants and penicillin antibiotics have been widely used in practice withoutreports of interaction. However, in the literature there are cases of increased internationalnormalised ratio in patients maintained on acenocoumarol or warfarin and prescribed acourse of amoxicillin. If co-administration is necessary, the prothrombin time orinternational normalised ratio should be carefully monitored with the addition or withdrawalof amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary(see section 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 andprolonged blood levels of amoxicillin but not of clavulanic acid.

Mycophenolate mofetil
In patients receiving mycophenolate mofetil, reduction in pre-dose concentration of theactive metabolite mycophenolic acid (MPA) of approximately 50% has been reportedfollowing commencement of oral amoxicillin plus clavulanic acid. The change in pre-doselevel may not accurately represent changes in overall MPA exposure. Therefore, a change inthe dose of mycophenolate mofetil should not normally be necessary in the absence ofclinical evidence of graft dysfunction. However, close clinical monitoring should beperformed 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 notindicate an increased risk of congenital malformations. In a single study in women withpreterm, premature rupture of the foetal membrane it was reported that prophylactictreatment with amoxicillin/clavulanic acid may be associated with an increased risk ofnecrotising enterocolitis in neonates. Use should be avoided during pregnancy, unlessconsidered essential by the physician.

Breastfeeding
Both substances are excreted into breast milk (nothing is known of the effects of clavulanicacid on the breast-fed infant). Consequently, diarrhoea and fungus infection of the mucousmembranes are possible in the breast-fed infant, so that breast-feeding might have to bediscontinued. 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 influencethe ability to drive and use machines.

4.8 Undesirable effects

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
Aseptic 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
Renal and urinary disorders	
Interstitial nephritis	Not known
Crystalluria[8]	Not known

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 intravenousadministration 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/electrolytebalance.
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 moreenzymes (often referred to as penicillin-binding proteins, PBPs) in the biosynthetic pathwayof bacterial peptidoglycan, which is an integral structural component of the bacterial cellwall. Inhibition of peptidoglycan synthesis leads to weakening of the cell wall, which isusually followed by cell lysis and death.

Amoxicillin is susceptible to degradation by beta-lactamases produced by resistant bacteriaand therefore the spectrum of activity of amoxicillin alone does not include organismswhich produce these enzymes.
Clavulanic acid is a beta-lactam structurally related to penicillins. It inactivates some betalactamaseenzymes 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 themajor 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.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Bothcomponents 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 bothcomponents are similar and the time to peak plasma concentration (Tmax) in each case is approximately onehour.

The pharmacokinetic results for a study, in which amoxicillin/clavulanic acid (875 mg/125 mg tablets giventwice daily) was administered in the fasting state to groups of healthy volunteers are presented below.

Mean (± SD) pharmacokinetic parameters

Active substance(s) administered	Dose (mg)	C_{max} (µg/ml)	T_{max} * (h)	$AUC_{(0-24h)}$ ((µg.h/ml)	T 1/2 (h)
Amoxicillin					
AMX/CA 875 mg/125 mg	875	11.64 ± 2.78	1.50 (1.0-2.5)	53.52 ± 12.31	1.19 ± 0.21
Clavulanic acid					
AMX/CA 875 mg/125 mg	125	2.18 ± 0.99	1.25 (1.0-2.0)	10.16 ± 3.04	0.96 ± 0.12

AMX – amoxicillin, CA – clavulanic acid
* Median (range)

Amoxicillin and clavulanic acid serum concentrations achieved with amoxicillin/clavulanic acid are similarto 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. Theapparent 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 notadequately distribute into the cerebrospinal fluid.

From animal studies there is no evidence for significant tissue retention of drug-derived material for eithercomponent. Amoxicillin, like most penicillins, can be detected in breast milk. Trace quantities of clavulanicacid 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 10to 25% of the initial dose. Clavulanic acid is extensively metabolized in man and eliminated in urine andfaeces 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 bothrenal and non-renal mechanisms.

Amoxicillin/clavulanic acid has a mean elimination half-life of approximately one hour and a mean totalclearance of approximately 25 l/h in healthy subjects. Approximately 60 to 70% of the amoxicillin andapproximately 40 to 65% of the clavulanic acid are excreted unchanged in urine during the first 6 h afteradministration of single Oxynic250 mg/125 mg or 500 mg/125 mg tablets. Various studies have foundthe urinary excretion to be 50-85% for amoxicillin and between 27-60% for clavulanic acid over a 24 hourperiod. In the case of clavulanic acid, the largest amount of drug is excreted during the first 2 hours afteradministration.
Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanicacid (see section 4.5).

Age
The elimination half-life of amoxicillin is similar for children aged around 3 months to 2 years and olderchildren and adults. For very young children (including preterm newborns) in the first week of life theinterval of administration should not exceed twice daily administration due to immaturity of the renalpathway of elimination. Because elderly patients are more likely to have decreased renal function, careshould 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, genderhas 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 renalfunction. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as ahigher proportion of amoxicillin is excreted via the renal route. Doses in renal impairment must thereforeprevent undue accumulation of amoxicillin while maintaining adequate levels of clavulanic acid (see section4.2).
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	Microcrystalline Cellulose	BP
2	Croscarmellose Sodium	BP
3	Colloidal Silicon Dioxide	BP
5	Sodium Starch Glycolate	BP

6	Sodium Lauryl Sulphate	BP
7	Magnesium Stearate	BP
8	Silicon dioxide	USP
9	Hydroxypropyl Methyl Cellulose	BP
10	Diethyl Phthalate	BP
11	Purified Talc	BP
12	Isopropyl Alcohol	BP
13	Dichloromethane	BP
14	Titanium Dioxide	BP

6.2 Incompatibilities

None known.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 25C. Protect from light & moisture. Keep out of reach of children.

6.5 Nature and contents of container

07 tablets are packed in one Alu Alu blister &such 02 blister are packed in a printed carton with insert.

6.6 Special precautions for disposal and other handling

Not applicable

7. Marketing authorization holder

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