# 1.11 SUMMARY OF PRODUCT CHARACTERISTICS

**OXYNIC 625** **GB PHARMA LIMITED**
(Amoxicillin and Potassium Clavulanate Tablets BP)

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## 1. NAME OF THE MEDICINAL PRODUCT

OXYNIC 625 (Amoxicillin and Potassium Clavulanate Tablets BP)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains

Amoxicillin Trihydrate BP

Eq. to Amoxicillin .....500 mg

Diluted Potassium Clavulanate BP

Eq. to Clavulanic acid……..125 mg

Excipients.....Q.S.

Colours: Approved colours used

## 3. PHARMACEUTICAL FORM

Film Coated Tablets.

02×07 tablets in Alu Alu Blister, packed in a printed carton with insert

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Oxynic 625 tablet is indicated for the treatment of the following infections in adults and children:

- Upper respiratory tract infections (including ENT): recurrent tonsillitis, acute sinusitis, acute otitis media.
- Lower respiratory tract infections: acute exacerbations of chronic bronchitis, community-acquired pneumonia.
- Urinary tract infections: cystitis (especially when recurrent or complicated – excluding prostatitis), pyelonephritis.
- Skin and soft tissue infections: cellulitis, animal bites and severe dental abscess with spreading cellulitis.
- Other infections: septic abortion, puerperal sepsis, intra-abdominal sepsis.

### 4.2 Posology and method of administration

Route of administration: oral use

Oxynic 625 tablet is not recommended for use in children below 12 years of age due to a lack of data on safety and efficacy.

Dosage depends on the age, weight and renal function of the patient and the severity of the infection. Dosages are expressed throughout in terms of amoxicillin-/clavulanate content except when doses are stated in terms of an individual component.

To minimise potential gastrointestinal intolerance, administer at the start of a meal. The absorption of amoxicillin clavulanate is optimised when taken at the start of a meal.

Treatment should not be extended beyond 14 days without review. Therapy can be started parenterally and continued with an oral preparation Usual dosage of amoxicillin-clavulanate in adults and adolescent 40 kg is one 500 mg/125 mg tablet taken two times a day.

**Usual dosages for the treatment of severe infections** is one 500/125 mg tablet taken three times a day. More suitable paediatric formulations of amoxicillin-clavulanate are available for the treatment in children.

**Elderly**

No adjustment needed; dose as for adults. If there is evidence of renal impairment, dose should be adjusted as for renally impaired adults.

**Renal impairment**

In patients with moderate or severe renal impairment, dosages should be adjusted according to the degree of impairment. Dosage adjustments are based on the maximum recommended level of amoxicillin.

| | |
|---|---|
| Creatinine clearance greater than 30 ml/min. | No adjustment necessary. |
| Creatinine clearance 10 to 30 ml/min . | One 500/125 mg tablet twice daily. |
| Creatinine clearance less than 10 ml /min. | Not recommended |

**Haemodialysis**

One 500/125 mg tablet every 24 h, PLUS one 500/125 mg tablet during dialysis, to be repeated at the end of dialysis (as serum concentrations of both amoxicillin and clavulanic acid are decreased).

**Hepatic impairment**

Dose with caution; monitor hepatic function at regular intervals. There are insufficient data on which to base a dosage recommendation

**4.3 Contraindications**

Amoxicillin-clavulanate is contraindicated in patients with a history of hypersensitivity to beta-lactams, e.g. penicillins and cephalosporins and to any of the excipients. In patients with a previous history of amoxicillin-clavulanate-associated jaundice/hepatic dysfunction.

**4.4 Special warnings and precautions for use**

Prolonged use may also occasionally result in overgrowth of non-susceptible organisms. Before initiating therapy with amoxicillin-clavulanate, 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 (see contraindications).

Change in liver function tests have been observed in some patients receiving Oxynic 625 .The clinical significance of these changes is uncertain but Oxynic 625 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 several weeks after treatment has ceased. In patients with renal impairment, dosage should be adjusted according to the degree of impairment (see Dosage and Administration– Renal impairment).

Oxynic 625 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.

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

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 (see Overdosage). Each Co-amoxiclav 500 mg/125 mg film- coated tablets contains 25 mg (i.e. 0.64 mmol) of potassium.

**4.5 Interaction with other medicinal products and other forms of interaction**

Concomitant use of probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin. Concomitant use with amoxicillin-clavulanate may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Prolongation of bleeding time and prothrombin time have been reported in some patients receiving Oxynic 625. Oxynic 625 should be used with care in patients on anti-coagulation therapy.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions. There are no data on the concomitant use of amoxicillin-clavulanate and allopurinol.

In common with other antibiotics, amoxicillin-clavulanate may affect the gut flora, leading to lower oestrogen reabsorption and reduced efficacy of combined oral contraceptives.

**4.6 Pregnancy and lactation**

This product should only be used in pregnancy or lactation if considered essential by the physician. Reproduction studies in animals (mice and rats at doses up to 10 times the human dose) with orally and parenterally administered amoxicillin-clavulanate have shown no teratogenic effects.

In a single study in women with preterm, premature rupture of the foetal membrane (pPROM), it was reported that prophylactic treatment with amoxicillin-clavulanate may be associated with an increased risk of necrotising enterocolitis in neonates.

Oxynic 625 may be administered during the period of lactation. With the exception of the risk of sensitization, associated with the excretion of trace quantities in breast milk, there are no known detrimental effects for the breast-fed infant.

**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: Reversible leucopenia (including neutropenia) and thrombocytopenia

Very rare: Reversible agranulocytosis and haemolytic anaemia. Prolongation of bleeding time and prothrombin time

Immune system disorders

Very rare: Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis

Nervous system disorders

Uncommon: Dizziness, headache

Very rare: Reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

Gastrointestinal disorders

Very common: Diarrhoea Common: Nausea, vomiting

Uncommon: Indigestion

Very rare: Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), black hairy tongue.

Hepato-biliary disorders

Uncommon: A moderate rise in AST and/or ALT and alkaline phosphatase has been noted in patients treated with beta-lactam class antibiotics, but the significance of these findings is unknown. Very rare: Hepatitis and cholestatic jaundice. These events have been noted with other penicillins and cephalosporins. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment.

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.

Skin and subcutaneous tissue disorders

Uncommon: Skin rash, pruritus, urticaria Rare: Erythema multiforme

Very rare: Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP).

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued.

Renal and urinary disorders

Very rare: Interstitial nephritis, crystalluria.

**4.9 Overdose**

Gastrointestinal symptoms and disturbance of the fluid and electrolyte balances may be evident. GI symptoms may be treated symptomatically, with attention to the water/electrolyte balance. Oxynic 625 can be removed from the circulation by haemodialysis. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see Section 4.4 Special warnings and special precautions for use)

**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

| Organism | Susceptibility Breakpoints (μg/ml) | | |
|---|---|---|---|
| | Susceptible | Intermediate | Resistant |

| | | | |
|---|---|---|---|
| *Streptococcus pneumoniae* | ≤ 0.5 | 1-2 | > 2 |
| *Haemophilus influenzae* | ≤ 1 | - | > 1 |
| *Staphylococcus spp.* | ≤ 4 | - | ≥ 8 |
| *Enterobacteriaceae* | - | - | > 8 |

[1] Breakpoint values in the table are based on ampicillin breakpoints.
[2] The reported values are for Amoxicillin concentrations. For susceptibility testing purposes, the concentration of clavulanic acid is fixed at 2 mg/l
[3] CLSI breakpoints (no intermediate value is specified). Staphylococci which are susceptible to amoxicillin/clavulanic acid but resistant to methicillin/oxacillin must be considered as resistant.
[4] The resistant breakpoint of R>8 mg/L ensures that all isolates with resistance mechanisı are reported resistant.

There are two main mechanisms of resistance to beta-lactam antibiotics, i.e. target (PBP) alteration and inactivation by beta-lactamases. Less often impermeability or efflux pump mechanisms may cause or contribute to bacterial resistance.

Breakpoints

MIC breakpoints for amoxicillin/clavulanic acid are those of the European Committee on Antimicrobial Susceptibility Testing (EUCAST)

Te 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>*Bacillus anthracis*<br>*Corynebacterium species*<br>*Enterococcus faecalis*<br>*Enterococcus faecium*<br>*Listeria monocytogenes*<br>*Nocardia asteroides*<br>*Staphylococcus aureus*<br>*Coagulase negative staphylococci*<br>*Streptococcus agalactiae*<br>*Streptococcus pneumoniae S*<br>*treptococcus pyogenes*<br>*Streptococcus species*<br>*Streptococcus viridans* |
| Anaerobic Gram-positive micro-organisms<br>*Clostridium species*<br>*Peptococcus species*<br>*Peptostreptococcus species* |

| |
|---|
| Aerobic Gram-negative micro-organisms<br>*Bordetella pertussis*<br>*Brucella species*<br>*Escherichia coli*<br>*Gardnerella vaginalis*<br>*Haemophilus influenzae*<br>*Helicobacter pylori Klebsiella species*<br>*Legionella species*<br>*Moraxella catarrhalis (Branhamella catarrhalis)*<br>*Neisseria gonorrhoeae*<br>*Neisseria meningitidis*<br>*Pasteurella multocida Proteus mirabilis*<br>*Proteus vulgaris*<br>*Salmonella species*<br>*Shigella species*<br>*Vibrio cholerae*<br>*Yersinia enterocolitica* |
| Anaerobic Gram-negative micro-organisms<br>*Bacteroides species (including Bacteroides fragilis)*<br>*Fusobacterium species*<br>Other micro-organisms<br>*Borrelia burgdorferi*<br>*Chlamydiae*<br>*Leptospira icterohaemorrhagiae*<br>*Treponema pallidum* |
| **Species for which acquired resistance may be a problem**<br>Aerobic Gram-positive micro-organisms<br>*Enterococcus faecium*<br>Aerobic Gram-negative micro-organisms<br>*Escherichia coli*<br>*Klebsiella sp.*<br>*Shigella sp.*<br>*Salmonella sp.*<br>*Yersinia enterocolitica*<br>**Inherently resistant micro-organism**<br>Aerobic Gram-positive micro-organisms<br>*Methicillin-resistant staphylococci*<br>Aerobic Gram-negative micro-organisms<br>*Pseudomonas sp.*<br>*Stenotrophomonas multophilia*<br>*Acinetobacter spp.*<br>*Serratia spp.* |

**5.2 Pharmacokinetic properties**

Absorption

The two components, of amoxicillin-clavulanate, 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-clavulanate is optimised when taken at the start of a meal

Distribution

Following i.v. administration, therapeutic concentrations of both amoxicillin and clavulanic acid may be detected in the tissues and interstitial fluid. Therapeutic concentrations of both drugs have been found in gall bladder, abdominal tissue, skin, fat, and muscle tissues; fluids found to have therapeutic levels include synovial and peritoneal fluids, bile and pus.

Neither amoxicillin nor clavulanic acid is highly protein bound, studies show that about 25% for clavulanic acid and 18% for amoxicillin of total plasma drug content is bound to protein. From animal studies there is no evidence to suggest that either component accumulates in any organ.

Oxynic 625 , like most penicillins, can be detected in breast milk. Trace quantities of clavulanate can also be detected in breast milk. With the exception of the risk of sensitisation associated with this excretion, there are no known detrimental effects for the breast-fed infant. Reproduction studies in animals have shown that both amoxicillin and clavulanic acid penetrate the placental barrier. However, no evidence of impaired fertility or harm to the foetus was detected.

Biotransformation

Amoxicillin is partly excreted in the urine as the inactive penicilloic acid in quantities equivalent to 10 to 25% of the initial dose. Clavulanic acid is extensively metabolized in man to 2,5-dihydro-4-(2-hydroxyethyl)-5-oxo-1H-pyrrole-3- carboxylic acid and 1-amino-4-hydroxy-butan-2-one and eliminated in urine and faeces as carbon dioxide in expired air.

Elimination

As with other penicillins, the major route of elimination for amoxicillin is via the kidney, whereas for clavulanate it is by both renal and non-renal mechanisms. 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 a single 250/125 mg or a single 500/125 mg tablet. Concomitant use of probenecid delays amoxicillin excretion but does not delay renal excretion of clavulanic acid (see Interactions).

**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 |
| 4 | Sodium Starch Glycolate | BP |
| 5 | Sodium Lauryl Sulphate | BP |
| 6 | Magnesium Stearate | BP |
| 7 | Ethyl Cellulose | BP |
| 8 | Hydroxypropyl Methyl Cellulose | BP |
| 9 | Diethyl Phthalate | BP |
| 10 | Purified Talc | BP |
| 11 | Isopropyl Alcohol | BP |
| 12 | Dichloromethane | BP |
| 13 | Titanium Dioxide | BP |

### 6.2 Incompatibilities

None known.

### 6.3 Shelf life

24 months

### 6.4 Special precautions for storage

Store below $25^0$C. 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

| | |
|---|---|
| Company Name | : GB PHARMA LIMITED |
| Address | : 65 Chatsworth Road, London NW2,4BG |
| Country | : United Kingdom |
| Phone | : +44 (0)2088301057 |
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## 8. Date of Publication or Revision

**NA**