Professional Information for Medicines for Human Use:

AMOXY CO 1000/200 and 500/100 GDC

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AMOXY CO 500/100 GDC sterile powder for injection

AMOXY CO 1000/200 GDC sterile powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AMOXY CO 500/100 GDC:

Each vial contains amoxicillin sodium equivalent to 500 mg amoxicillin and potassium clavulanate equivalent to 100 mg clavulanic acid.

Sodium content: 31,45 mg (1,37 mmol) per vial.

Potassium content: 19,625 mg (0,5 mmol) per vial.

Sugar free.

AMOXY CO 1000/200 GDC:

Each vial contains amoxicillin sodium equivalent to 1000 mg amoxicillin and potassium clavulanate equivalent to 200 mg clavulanic acid.

Sodium content: 62,90 mg (2,74 mmol) per vial.

Potassium content: 39,25 mg (1,0 mmol) per vial.

Sugar free.

For the full list of excipients, see section 6.1.

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3. PHARMACEUTICAL FORM

Sterile powder for injection.

AMOXY CO 500/100:

White or almost white powder in 10 mL clear EP type II glass vials.

AMOXY CO 1000/200:

White or almost white powder in 20 mL clear EP type II glass vials.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AMOXY CO GDC is indicated when oral formulations cannot be used for the treatment of infections, caused by amoxicillin resistant organisms producing beta-lactamase sensitive to clavulanic acid:

- Upper respiratory tract infections such as sinusitis, recurrent otitis media, tonsillitis.
- Lower respiratory tract infections, such as bronchitis and bronchopneumonia
- Genito-urinary tract infections, such as cystitis, urethritis, pyelonephritis
- Skin and soft tissue infections.

AMOXY CO GDC will also be effective in the treatment of infections caused by amoxicillin sensitive organisms, at appropriate amoxicillin dosages, since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

4.2 Posology and method of administration

Posology

General information

For infections caused by amoxicillin sensitive organisms the dosage is that approved for amoxicillin, as the clavulanic acid component does not contribute to the therapeutic effect.

Adults

For severe infections of the respiratory tract, urinary tract and skin and soft tissue requiring parenteral therapy initially one AMOXY CO 1000/200 GDC vial containing the equivalent of 1000 mg amoxicillin and 200 mg clavulanic acid, can be administered intravenously 6 to 8 hourly by intravenous injection (2 minutes) or intravenous infusion (30 minutes) until the condition settles followed by oral therapy at the recommended dose.

If no response is obtained within 48 hours therapy must be reviewed.
Intravenous treatment with AMOXY CO GDC should not be extended beyond 10 days without review and the total daily administration of clavulanic acid should not exceed 800 mg.

Treatment can be continued orally where appropriate after a satisfactory therapeutic response has been obtained.

Dosage guide

AMOXICILLIN SENSITIVE ORGANISMS				
Product	**Upper Respiratory Tract**	**Lower Respiratory tract**	**Urinary Tract Infections**	**Skin & Soft Tissue Infections**

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	Infections	**Infections**		
Adults				
AMOXY CO 1000/200 GDC	1 vial [(a)] 6 - 8 hourly	1 vial [(a)] 6 - 8 hourly	1 vial [(a)] 6 - 8 hourly	1 vial [(a)] 6 - 8 hourly
AMOXY CO 500/100 GDC	-	-	2 vials [(a)] 6 - 8 hourly	2 vials [(a)] 6 - 8 hourly

AMOXICILLIN RESISTANT ORGANISMS				
Product	**Upper Respiratory Tract Infections**	**Lower Respiratory tract Infections**	**Urinary Tract Infections**	**Skin & Soft Tissue Infections**
Adults				
AMOXY CO 1000/200 GDC	1 vial [(a)] 6 - 8 hourly	1 vial [(a)] 6 - 8 hourly	1 vial [(a)] 6 - 8 hourly	1 vial [(a)] 6 - 8 hourly
AMOXY CO 500/100 GDC	-	-	2 vials [(a)] 6 - 8 hourly	2 vials [(a)] 6 - 8 hourly

[(a)] Intravenous therapy should not be continued for longer than 10 days.

Renal impairment

Each AMOXY CO 500/100 GDC vial contains 0,5 mmol of potassium and 1,37 mmol of sodium.

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Each AMOXY CO 1000/200 GDC vial contains 1,0 mmol of potassium and 2,74 mmol of sodium.

As the kidneys excrete both the amoxicillin and clavulanic acid components of AMOXY CO GDC, accumulation of both may occur in patients with renal insufficiency. In these cases, monitoring of the serum levels and a reduction in the number of administrations of the suggested dosage may be required.

Experience in a limited number of patients with varying degrees in renal insufficiency suggest that the following schedule of dosage based on the creatinine clearance of the patient may be used as a guideline:

Creatinine clearance	**Dosage**
> 30 mL/min	No dosage adjustment
10 – 30 mL/min	1,2 g AMOXY CO GDC initially and then 600 mg 12 hourly
< 10 mL/min	1,2 g AMOXY CO GDC initially and then 600 mg daily

Hepatic impairment

Dose with caution and monitor hepatic function at regular intervals (see sections 4.3 and 4.4).

Paediatric population

Insufficient evidence exists at present to recommend an intravenous dosage in children.

Method of administration

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AMOXY CO GDC is for intravenous use and is not suitable for intramuscular or subcutaneous administration.

The reconstituted vial can be administered intravenously by injection (2 minutes) or slow intravenous infusion (30 minutes). Infusion should be completed within the period of stability of AMOXY CO GDC infusions after reconstitution and dilution, as reflected in the table under the section “Compatibility of AMOXY CO GDC with IV fluids and stability of reconstituted solution” presented in section 6.6. The contents of the vial must be used within 20 minutes and thereafter any unused material should be discarded.

Please refer to section 6.6 below for “Preparation of solutions for intravenous injection and intravenous infusion”.

4.3 Contraindications

- Hypersensitivity to the active substances or any excipients listed in section 6.1.
- Patients with a history of hypersensitivity (e.g. anaphylaxis) to beta-lactam antibiotics such as penicillins, cephalosporins, carbapenems or to monobactams. Cross-sensitivity between penicillins and cephalosporins is well documented.
- Patients that have a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.
- Safety and efficacy in children have not been established with AMOXY CO GDC.

4.4 Special warnings and precautions for use

Hypersensitivity

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Before initiating therapy with AMOXY CO GDC, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other beta- lactam medicines (see sections 4.3 and 4.8). Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins.

Serious and occasional fatal hypersensitivity reactions (including anaphylactoid and severe cutaneous adverse reactions such as Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS)) have been reported in patients on penicillin therapy.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction (see section 4.8). These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and in atopic individuals. There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins.

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate as in AMOXY CO GDC (see section 4.8). DIES is an allergic reaction with the leading symptom of protracted vomiting (1 - 4 hours after drug administration) in the absence of allergic skin or respiratory symptoms. Further symptoms could comprise abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock.

If an allergic reaction occurs, AMOXY CO GDC should be discontinued and the appropriate therapy instituted which may include epinephrine (adrenaline), intravenous corticosteroids

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and antihistamines. Oxygen and airway management, including intubation may also be required.

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).

Infectious mononucleosis

Since AMOXY CO GDC contains amoxicillin, an aminopenicillin, it is not the treatment of choice in patients presenting with sore throat or pharyngitis because of the possibility that the underlying cause is infectious mononucleosis, in the presence of which there is a high incidence of morbilliform rash if amoxicillin is used. AMOXY CO GDC should be avoided if infectious mononucleosis is suspected.

Prolonged use, overgrowth and antibiotic associated colitis

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

Prolonged use may result in overgrowth of non-susceptible organisms. The possibility of superinfections with mycotic or bacterial pathogens should be kept in mind during therapy. If superinfections occur (usually involving *Aerobacter, Pseudomonas* or *Candida*), AMOXY CO GDC should be discontinued and/or appropriate therapy instituted.

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Antibiotic-associated colitis, such as Pseudomembranous enterocolitis and haemorrhagic colitis, has been reported with nearly all antibacterial medicines including amoxicillin and may range in severity from mild to life threatening (see section 4.8).

Therefore, AMOXY CO GDC should be used with caution in patients with a history of gastrointestinal disease, especially antibiotic associated colitis. 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, AMOXY CO GDC should immediately be discontinued, a doctor be consulted, and an appropriate therapy initiated. Antiperistaltic medicines are contraindicated in this situation.

Acute generalised exanthemous pustulosis (AGEP)

The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis (AGEP) (see section 4.8). This reaction requires AMOXY CO GDC discontinuation and contraindicates any subsequent administration of amoxicillin.

Hepatic impairment

AMOXY CO GDC acid should be used with caution in patients with evidence of hepatic impairment (see sections 4.2, 4.3 and 4.8).

Changes in liver function tests, transient hepatitis and cholestatic jaundice have been reported.

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Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. These events have been less frequently 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 medicines known to have the potential for hepatic effects (see section 4.8).

Renal impairment

In patients with moderate or severe renal impairment, the dose should be adjusted according to the degree of impairment (see section 4.2).

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed less frequently, 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 (see sections 4.8 and 4.9).

Concomitant use with anticoagulants

Prolongation of prothrombin time has been reported less frequently in patients receiving amoxicillin/clavulanic acid as in AMOXY CO GDC. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly. Adjustments in the dose of

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oral anticoagulants may be necessary to maintain the desired level of anticoagulation (see sections 4.5 and 4.8).

Patients with syphilis

Caution is needed when administering amoxicillin to patients with syphilis, as the Jarisch-Herxheimer reaction may occur in these patients.

Patients with lymphatic leukaemia

AMOXY CO GDC should be given with caution to patients with lymphatic leukaemia, since they are especially susceptible to amoxicillin-induced skin rashes.

Resistance

The use of AMOXY CO GDC may lead to the selection of resistant strains of organisms and sensitivity testing should, therefore, be carried out whenever possible, to demonstrate the appropriateness of therapy.

Laboratory tests

Glucose test

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 (e.g., chemical methods).

Coombs test

The presence of clavulanic acid in AMOXY CO GDC may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

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Aspergillus test

There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving amoxicillin/clavulanic acid as in AMOXY CO GDC 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 AMOXY CO GDC should be interpreted cautiously and confirmed by other diagnostic methods.

Sodium and potassium

AMOXY CO 500/100 GDC contains 31,45 mg sodium per vial, equivalent to 1,57 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
AMOXY CO 500/100 GDC contains potassium, less than 1 mmol (39 mg) per vial, i.e. essentially ‘potassium-free’.

AMOXY CO 1000/200 GDC contains 62,90 mg sodium, equivalent to 3,15 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.
AMOXY CO 1000/200 GDC contains 1 mmol (or 39,25 mg) potassium per vial. To be taken into consideration by patients with reduced kidney function or patients on a controlled potassium diet.

4.5 Interaction with other medicines and other forms of interaction

Probenecid

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Concomitant use of probenecid is not recommended. Concurrent use of probenecid with AMOXY CO GDC may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

Oral contraceptives

Following administration of ampicillin to pregnant woman a transient decrease in plasma concentration of total conjugate estriol, estriol-glucuronide, conjugated estrone and estradiol has been noted. This effect may also occur with AMOXY CO GDC leading to lower estrogen re-absorption and reduced efficacy of combined oral contraceptives. Patients should be warned accordingly.

Allopurinol

The concomitant administration of allopurinol and amoxicillin substantially increases the incidence of skin rashes in patients receiving both agents as compared to patients receiving AMOXY CO GDC alone. It is not known whether this potentiation of AMOXY CO GDC rashes is due to allopurinol or the hyperuricaemia present in these patients.

Tetracyclines and other bacteriostatics

Tetracyclines and other bacteriostatic drugs may interfere with the bactericidal effects of AMOXY CO GDC.

Methotrexate

Penicillins may reduce the excretion of methotrexate causing a potential increase in toxicity.

Mycophenolate mofetil

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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.

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 (INR) in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin as in AMOXY CO GDC. If co- administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of AMOXY CO GDC. Moreover, adjustments in the dose of oral anticoagulants may be necessary (see section 4.4 and 4.8).

Alcohol

No information is available about the concurrent use of AMOXY CO GDC and alcohol.

However, the ingestion of alcohol whilst being treated with some other beta-lactam antibiotics has precipitated a disulfiram-like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with AMOXY CO GDC.

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4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of AMOXY CO GDC in pregnancy has not been established.

In women with pre-term, 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. Use of AMOXY CO GDC should be avoided during pregnancy.

Breastfeeding

Both amoxicillin and clavulanic acid are distributed into breast milk (nothing is known of the effects of clavulanic acid on the breast-fed infant). The use of AMOXY CO GDC by nursing mothers may lead to sensitisation, diarrhoea, candidiasis and skin rashes in the infant. Mothers on treatment with AMOXY CO GDC should not breastfeed their infants.

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. Since adverse reactions such as allergic reactions, dizziness, convulsions have been reported in patients receiving co-amoxiclav as in AMOXY CO GDC, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain AMOXY CO GDC does not adversely affect their ability to do so (see sections 4.4 and 4.8).

4.8 Undesirable effects

a. Summary of the safety profile

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The most frequently reported adverse drug reactions are mucocutaneous candidiasis, diarrhoea, nausea and vomiting.

Life-threatening skin adverse reactions such as the Stevens-Johnson and Lyell's syndromes (the latter is also known as toxic epidermal necrolysis (TEN)) and severe and sometimes fatal hepatic events have been reported with an unknown frequency (see section 4.4).

b. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Adverse reactions**
Infections and infestations	Frequent	mucocutaneous candidiasis (including vaginitis, stomatitis, glossitis)
	Frequency unknown	overgrowth of non-susceptible organisms
Blood and lymphatic system disorders	Less frequent	reversible leukopenia (including neutropenia), thrombocytopenia
	Frequency unknown	reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time* (see section 4.4)

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Immune system disorders	Frequency unknown	angioedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis
Nervous system disorders	Less frequent	dizziness, headache
	Frequency unknown	convulsions (see section 4.4)*, aseptic meningitis
Cardiac disorders	Frequency unknown	Kounis syndrome
Vascular disorders	Less frequent	thrombophlebitis at the site of injection
Gastrointestinal disorders	Frequent	diarrhoea*
	Less frequent	nausea*, vomiting, indigestion, gastritis
	Frequency unknown	antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis) (see section 4.4), drug-induced enterocolitis syndrome (DIES), acute pancreatitis
Hepatobiliary disorders	Less frequent	increase in liver enzymes (AST and/or ALT)
	Frequency unknown	hepatitis*, cholestatic jaundice* (see section 4.4)
Skin and subcutaneous tissue disorders*	Less frequent	skin rash, pruritus, urticaria, erythema multiforme
	Frequency unknown	Stevens-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN), bullous exfoliative-dermatitis, acute generalised exanthemous pustulosis (AGEP),

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		drug reaction with eosinophilia and systemic symptoms (DRESS), linear IgA disease
Renal and urinary disorders	Less frequent	interstitial nephritis, crystalluria (including acute renal injury) (see section 4.9)
General disorders and administration site conditions	Frequency unknown	local irritation, induration and phlebitis at the injection site.

*See below section c for description of selected adverse reactions.

c. Description of selected adverse reactions

Life-threatening skin adverse reactions

AMOXY CO GDC may cause life-threatening cutaneous reactions Steven-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) also known as Lyell's syndrome and drug reaction with eosinophilia and systemic symptoms (DRESS),

If symptoms or signs of SJS, TEN and DRESS (e.g., progressive skin rash often with blisters or mucosal lesions) are present, AMOXY CO GDC treatment should be

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discontinued immediately because the danger of severe allergic reactions (see section 4.8).

Hepatic events

Hepatic events may be severe and fatal. 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 events have been noted with other penicillins and cephalosporins (see also sections 4.2 and 4.4).

Convulsions

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.4).

Gastrointestinal side effects

The incidence and severity of frequent and less frequent gastrointestinal adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering AMOXY CO GDC at the start of a meal. In addition, as these symptoms are especially related to the potassium clavulanate component, where these gastrointestinal symptoms occur and a higher concentration of amoxicillin is required, consideration should be given to administering the additional amoxicillin separately.

Prolongation of bleeding time and prothrombin time (increased INR).

Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly with AMOXY CO GDC (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

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Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Alternately you can contact Gulf Drug Company (Pty) Ltd at +27 31 538 8700 or per info@gulfdrug.co.za.

4.9 Overdose

Symptoms and signs

Gastrointestinal symptoms such as nausea, vomiting and diarrhoea and disturbance of the fluid and electrolyte balances may be evident. Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see sections 4.4 and 4.8).

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.4).

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

Gastrointestinal symptoms may be treated symptomatically, with attention to the water/electrolyte balance.

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Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria.

Amoxicillin and clavulanic acid may be removed from the circulation by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and Class: A 20.1.2 Penicillins

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors.

ATC code: J01CR02.

Mechanism of action

The amoxicillin component of the formulations exert a bactericidal action against many strains of Gram-positive and Gram-negative organisms. The clavulanic acid component has very little bactericidal action. It does however, by inactivation of susceptible beta-lactamases, protect amoxicillin from degradation by a large number of beta-lactamase enzymes produced by penicillin resistant strains of organisms. Potassium clavulanate has been shown in vitro to be an irreversible inhibitor of beta-lactamases.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of amoxicillin and clavulanic acid are closely allied. Doubling the dose virtually doubles the peak serum level.

Distribution

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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
(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 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 elimination half-life of amoxicillin is approximately 1 hour. Small amounts of amoxicillin are excreted in the faeces and bile.

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Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation.

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 a single 500 mg/100 mg or a single 1000 mg/200 mg bolus intravenous injection. 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 (see section 4.5).

Age

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.

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

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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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

AMOXY CO GDC must not be mixed with other medicines except those mentioned in section 6.6.

AMOXY CO GDC powder for solution for injection/infusion or reconstituted solution should not be mixed with

- blood products
- other proteinaceous fluids such as protein hydrolysates
- intravenous lipid emulsions
- glucose
- dextran
- bicarbonate.

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If AMOXY CO GDC is prescribed concomitantly with an aminoglycoside, the antibiotics should not be mixed in the syringe, intravenous fluid container or giving set because substantial loss of activity of the aminoglycoside can occur under these conditions.

6.3 Shelf life

Powder in vials

3 years.

Reconstituted vials for intravenous injection or before dilution for infusion

Chemical and physical in-use stability has been demonstrated for 4 hours at 25 °C or 4 hours at 4 °C.

Reconstituted solution for intravenous infusion

Chemical and physical in-use stability has been demonstrated for 4 hours at 4 hours at 4 °C.

From a microbiological point of view, the reconstituted injection and diluted solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Powder in vials

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Store at or below 25 ºC. Protect from light and moisture. Do not freeze.

Do not remove vials from unit carton until required for use.

Reconstituted solution to be stored in original vials

Solutions reconstituted with water for injection should be used within 4 hours if kept at 25 ºC or 4 ºC.

Reconstituted solution for intravenous infusion

Solutions reconstituted with water for injection and then prepared for infusion in sodium chloride 0,9 % *w/v*, should be used within 4 hours if kept at 4 ºC.

6.5 Nature and contents of container

AMOXY CO 500/100 GDC:

White printed unit carton containing 10 clear glass EP type II vials with a grey bromobutyl stopper EP Type I and a purple polypropylene and aluminium flip-off cap.

AMOXY CO 1000/200 GDC:

White printed unit carton containing 10 clear glass EP type II vials with a red chlorobutyl stopper EP Type I and a purple polypropylene and aluminium flip-off cap.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For single use only. Discard any unused solution.

Reconstitution/dilution must be carried out under aseptic conditions. The solution is to be inspected visually for particulate matter and discoloration prior to administration. The solution should only be used if the solution is clear and free from particles.
Any unused medicine or waste material should be discarded.

Compatibility of AMOXY CO GDC with IV fluids and stability of reconstituted solution

The period of stability of AMOXY CO GDC infusion fluids after being reconstituted and diluted are as follows:

STRENGTH	**INFUSION FLUID**	**VOLUME OF FLUID INFUSION (mL)**		**STABILITY (hours)**	
		AMOXY CO 500/100 GDC	**AMOXY CO 1000/200 GDC**	**4 °C**	**25 °C**
AMOXY CO 500/100 GDC: 1 vial reconstituted with 10 mL Water for Injection	Water for Injection	50	100	4	4
	Sodium chloride Intravenous injection BP (0,9 % *w/v*)	50	100	4	-
AMOXY CO 1000/200 GDC: 1 vial reconstituted	Water for Injection	50	100	4	4
	Sodium chloride	50	100	4	-

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with 20 mL Water for Injection	Intravenous injection BP (0,9 % *w/v*)				

*For storage at 4 °C, the reconstituted solutions should be added to a pre-refrigerated bag of infusion fluid. In use, the solution should be allowed to reach room temperature and then administered without delay.

Preparation of solutions for intravenous injection

Water for Injection is the normal solvent. AMOXY CO GDC should be dissolved in the appropriate amount of solvent as mentioned below giving a solution for single-dose use.

AMOXY CO 500 mg/100 mg GDC should be dissolved in 10 mL of solvent.
AMOXY CO 1000 mg/200 mg GDC should be dissolved in 20 mL of solvent.

A transient pink colouration may or may not develop during reconstitution. After reconstitution, the solution in the vial is a clear pale-yellow colour, free from visible particles.

AMOXY CO GDC for bolus injection should be administered within 20 min of reconstitution.

Preparation of solutions for intravenous infusion

AMOXY CO GDC must be reconstituted as described above for injection. Without delay the reconstituted solution of AMOXY CO 500/100 GDC or AMOXY CO 1000/20 GDC should be added to 50 mL or 100 mL of sodium chloride intravenous infusion BP (0,9 % *w/v*), respectively using a minibag or in-line burette.

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A transient pink colouration may or may not develop during reconstitution.

Reconstituted solutions are normally colourless or is of a clear pale-yellow colour, free from visible particles.

Solutions for intravenous infusion should be administered in full within 4 hours of preparation if it had been kept at 4 °C or within 60 minutes of preparation.

AMOXY CO GDC vials are not suitable for multi-dose use.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Gulf Drug Company (Pty) Ltd

22 Burnside Drive

Old Mill Industrial Park

Mount Edgecombe

4300

8. REGISTRATION NUMBERS

AMOXY CO 500/100 GDC: 41/20.1.2/0977

AMOXY CO 1000/200 GDC: 41/20.1.2/0978

9. DATE OF FIRST AUTHORISATION

30 September 2011

10. DATE OF REVISION OF THE TEXT

03 April 2025

K. Holmes