Professional information for BINDOCLAV

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

BINDOCLAV 375 mg, tablet.

BINDOCLAV 625 mg, tablet.

BINDOCLAV 1 000 mg, tablet.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

BINDOCLAV 375 mg: Each film-coated tablet contains amoxicillin trihydrate equivalent to 250 mg amoxicillin, and potassium clavulanate equivalent to 125 mg clavulanic acid.

BINDOCLAV 625 mg: Each film-coated tablet contains amoxicillin trihydrate equivalent to 500 mg amoxicillin, and potassium clavulanate equivalent to 125 mg clavulanic acid.

BINDOCLAV 1 000 mg: Each film-coated tablet contains amoxicillin trihydrate equivalent to 875 mg amoxicillin, and potassium clavulanate equivalent to 125 mg clavulanic acid.

Sugar free.

For the full list of excipients, see **section 6.1.**

3. PHARMACEUTICAL FORM

BINDOCLAV 375 mg: White oval shaped film coated tablets, debossed with 'A' on one side and '63' on the other side.

BINDOCLAV 625 mg: White oval shaped film coated tablets, debossed with 'A' on one side and '64' on the other side.

BINDOCLAV 1 000 mg: White coloured, capsule shaped, film coated tablets, debossed with 'A' on one side and with a score line in between '6' and '5' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

BINDOCLAV formulations are indicated for the treatment of infections caused by amoxicillin resistant organisms producing beta-lactamases 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.
- BINDOCLAV formulations will also be effective in the treatment of infections caused by amoxicillin sensitive organisms at the appropriate amoxicillin dosage since in this situation the clavulanic acid component does not contribute to the therapeutic effect.

4.2 Posology and method of administration

Posology

Tablets should be taken immediately before a meal.

During the administration of amoxicillin, it is advisable to maintain adequate fluid intake and urinary output to prevent any possibility of amoxicillin crystalluria.

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

The adult dose of BINDOCLAV is one BINDOCLAV 375 mg tablet every eight hours at the start of a meal. For more severe infections and infection of the respiratory tract, the dose should be one

BINDOCLAV 625 mg tablet every eight hours at the start of a meal, or one BINDOCLAV 1 000 mg tablet every 12 hours at the start of a meal.

Since BINDOCLAV 375 mg, 625 mg and 1 000 mg tablets contain the same amount of clavulanic acid (125 mg as the potassium salt) two BINDOCLAV 325 mg tablets are not equivalent to one BINDOCLAV 625 mg tablet, and two BINDOCLAV 625 mg tablets are not equivalent to one BINDOCLAV 1 000 mg. Therefore, two BINDOCLAV 375 mg tablets should not be substituted for one BINDOCLAV 625 mg tablet or two BINDOCLAV 625 mg tablets for one BINDOCLAV 1 000 mg tablet for the treatment of more severe infections.

Dosage guide

Amoxicillin-sensitive organisms

Product	**Upper respiratory tract infection**	**Lower respiratory tract infection**	**Urinary tract infection**	**Skin & soft tissue infections**
BINDOCLAV 375 mg	1 Tablet 8 hourly	—	1 Tablet 8 hourly	1 Tablet 8 hourly
BINDOCLAV 625 mg	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly
BINDOCLAV 1000 mg	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly

Amoxicillin-resistant organisms

Product	**Upper respiratory tract infection (Otitis media)**	**Lower respiratory tract infection (Bronchitis)**	**Urinary tract infection**	**Skin & soft tissue infections**
BINDOCLAV	—	—	1 Tablet 8 hourly	1 Tablet 8 hourly

375 mg				
BINDOCLAV 625 mg	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly	1 Tablet 8 hourly
BINDOCLAV 1000 mg	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly	1 Tablet 12 hourly

Special populations

Renal impairment

The dose may need to be reduced or the interval extended. Dosage adjustments are based on the maximum recommended level of amoxicillin. The following schedule is proposed:

BINDOCLAV 375 mg, 625 mg:

- Mild impairment (creatinine clearance greater than 30 mL/minute): no change in dosage.
- Moderate impairment (creatinine clearance 10 to 30 mL/minute): 1 tablet every 12 hours.
- Severe impairment (creatinine clearance less than 10 mL/minute): half a tablet every 12 hours.

BINDOCLAV 1 000 mg should not be used in patients with glomerular filtration rate of less than 30 mL /minute.

Haemodialysis decreases serum concentrations of both amoxicillin and clavulanic acid and an additional dose should be administered at the end of dialysis.

Hepatic impairment

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

Paediatric population

The dose of BINDOCLAV in children is 25 – 50 mg/kg/day of the 4 parts amoxicillin, 1-part clavulanic acid preparations (which corresponds to a daily dosage of the equivalent of 20 – 40 mg/kg of amoxicillin and 5 – 10 mg/kg of clavulanic acid) to be taken in divided doses every eight hours, at the start of a meal.

Method of administration

Oral administration.

4.3 Contraindications

- Hypersensitivity to penicillins, cephalosporins or to any of the excipients listed in section 6.1. Cross-sensitivity between penicillins and cephalosporins is well documented.
- BINDOCLAV is contraindicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with BINDOCLAV, careful enquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins or other allergens. Although anaphylaxis is more frequent following parenteral therapy, it has occurred in patients on oral penicillins. These reactions are more likely to occur in individuals with a history of penicillin hypersensitivity and/or a history of sensitivity to multiple allergens. There have been reports of individuals with a history of penicillin hypersensitivity, who have experienced severe reactions when treated with cephalosporins.

Hypersensitivity reactions can also progress to Kounis syndrome, a serious allergic reaction that can result in myocardial infarction. Presenting symptoms of such reactions can include chest pain occurring in association with an allergic reaction to amoxicillin/clavulanic acid (see section 4.8).

If an allergic reaction occurs, BINDOCLAV should be discontinued, and the appropriate therapy instituted. Serious anaphylactic reactions may require immediate emergency treatment with adrenaline. Oxygen, intravenous steroids, and airway management, including intubation may also be required.

Overgrowth of non-susceptible organisms

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents including amoxicillin, as in BINDOCLAV, and may range in severity from mild to life threatening (see s**ection 4.8**). Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or after the administration of any antibiotics. Should antibiotic-associated colitis occur, BINDOCLAV should immediately be discontinued, a doctor must be consulted, and an appropriate therapy initiated. Anti-peristaltic medicines are contraindicated in this situation.

Prolongation of prothrombin time

Prolongation of prothrombin time has been reported rarely in patients receiving BINDOCLAV. 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 (see **sections 4.5** and **4.8**).

Periodic assessments

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

Impaired hepatic function

Transient hepatitis and cholestatic jaundice have been reported. BINDOCLAV should be used with caution in patients with evidence of hepatic dysfunction.

Changes in liver function tests have been observed in some patients receiving BINDOCLAV. It should be used with care in patients with evidence of severe hepatic dysfunction (see **sections 4.2** and **4.8**).

Impaired renal function

BINDOCLAV 1 000 mg should not be used in patients with a glomerular filtration rate of less than 30 mL/minute.

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

In patients with moderate or severe renal impairment BINDOCLAV dosage should be adjusted (see **section 4.2**).

Infections

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

Since BINDOCLAV 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 rash if amoxicillin is used.

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), the agent should be discontinued and/or appropriate 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 BINDOCLAV to amoxicillin in accordance with official guidance.

BINDOCLAV is 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 susceptible to inhibition by clavulanic acid. BINDOCLAV should not be used to treat penicillin-resistant *S. pneumoniae*.

Fluid intake

When high doses are administered, adequate fluid intake and urinary output must be maintained.

The sodium content must be taken into account in patients on a sodium-restricted diet if the

administration of high doses is necessary.

Maintaining an adequate fluid intake and urinary output is important to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see s**ection 4.9**).

Skin reactions

BINDOCLAV should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions (see **section 4.5**).

The occurrence at 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 BINDOCLAV discontinuation and contraindicates any subsequent administration of amoxicillin.

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially sodium-free.

4.5 Interaction with other medicines and other forms of interaction

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

BINDOCLAV may reduce the efficacy of oral contraceptives and patients should be warned

accordingly.

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

Tetracyclines and other bacteriostatic medicines may interfere with the bactericidal effects of amoxicillin.

If co-administration of BINDOCLAV with anticoagulant/s is necessary, the prothrombin time or international normalised ratio (INR) should be carefully monitored with the addition or withdrawal of amoxicillin as adjustments in the dose of oral anticoagulants may be necessary (see **section 4.4** and **4.8**).

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

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.

Interaction with laboratory tests

It is recommended that when testing for the presence of glucose in urine during BINDOCLAV treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary

concentrations of amoxicillin, false positive readings are common with chemical methods.

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

4.6 Fertility, pregnancy, and lactation

Pregnancy

BINDOCLAV should be avoided during pregnancy, as the safety of BINDOCLAV in pregnancy has not been established.

Breastfeeding

Amoxicillin and clavulanic acid, as in BINDOCLAV, are distributed into breast milk. Although significant problems in humans have not been documented, the use of amoxicillin by nursing mothers may lead to sensitisation, diarrhoea, candidiasis, and skin rash in the infant which may result in the discontinuation of BINDOCLAV.
Therefore, caution should be exercised when BINDOCLAV is administered to a nursing woman.
The use of BINDOCLAV 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.

Fertility

No data are available.

4.7 Effects on ability to drive and use machines

BINDOCLAV may cause headache, dizziness, allergic reactions, and convulsions which may impair the ability to drive a vehicle or operate machinery (see **section 4.8**). Patients should refrain from driving and using machinery until the effects of BINDOCLAV are known.

4.8 Undesirable effects

The most frequently reported adverse effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, genital moniliasis, abnormal taste, headache, dizziness, tiredness, and hot flushes.

The incidence and severity of adverse effects, particularly nausea and diarrhoea, increased with the higher recommended dose and can be minimised by administering BINDOCLAV 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.

The following adverse reactions have been reported and may occur with BINDOCLAV:

Infections and infestations

Frequent: Mucocutaneous candidiasis.

Frequency unknown: Overgrowth of non-susceptible organisms.

Blood and the lymphatic system disorders

Less frequent: Reversible leukopenia (including neutropenia), thrombocytosis, thrombocytopenia.

Frequency unknown: Haemolytic anaemia, prolongation of bleeding time and prothrombin time, , thrombocytopenic purpura, eosinophilia, reversible agranulocytosis.

Immune system disorders

Less frequent: Serum sickness-like syndrome

Frequency unknown: Angioneurotic oedema, anaphylaxis, hypersensitivity vasculitis.

Nervous system disorders

Frequent: Headache.

Less frequent: Convulsions, dizziness.

Frequency unknown: Reversible hyperactivity, aseptic meningitis.

Cardiac disorders

Less frequent: Kounis syndrome.

Gastrointestinal disorders

Frequent: Nausea, vomiting, diarrhoea.

Less frequent: Glossitis, black hairy tongue, indigestion.

Frequency unknown: Gastritis, stomatitis, enterocolitis, and antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis).

Hepato-biliary disorders

Less frequent: Hepatitis, cholestatic jaundice, increase in AST and/or ALT.

Skin and subcutaneous tissue disorders

Less frequent: Skin rash, pruritus, urticaria, erythema multiform, Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis (AGEP).

Frequency unknown: Bullous exfoliative dermatitis, drug reaction with eosinophilia and systemic symptoms (DRESS).

Renal and urinary disorders

Frequency unknown: Interstitial nephritis, crystalluria.

General disorders and administration site disorders

Frequency unknown: Superficial tooth discolouration, especially with the suspension and chewable tablet formulations. It can usually be removed by brushing.

Description of selected adverse reactions

Hypersensitivity reactions are usually reversible on discontinuation of therapy. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.
Whenever such reactions occur, BINDOCLAV should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see **section 4.4**).

Convulsions may occur with impaired renal function or in those receiving high doses.
Nausea is more often associated with higher oral doses. If gastro-intestinal reactions are evident, they may be reduced by taking BINDOCLAV at the start of a meal.

Hepatic events may be severe and occur predominantly in adults or elderly patients. 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.
The hepatic effects are usually reversible. However, in extremely rare circumstances, death has been reported. These have almost always been cases associated with serious underlying disease or concomitant medication.
A moderate rise in aspartate transaminase (AST) and/or alanine transaminase (ALT) has been noted in patients treated with BINDOCLAV, but the significance of these findings is unknown.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of BINDOCLAV is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to the South African Health Products Regulatory Authority (SAHPRA) via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website or to Cipla Medpro (Pty) Ltd. by email: drugsafetysa@cipla.com or telephone: 080 222 6662 (toll free).

4.9 Overdose

Overdosage with amoxicillin, as in BINDOCLAV, is usually asymptomatic. However, gastrointestinal effects such as nausea, vomiting and diarrhoea may be evident, and symptoms of water and electrolyte imbalance should be treated symptomatically.

Adequate fluid intake and urinary output must be maintained to minimise the possibility of crystalluria. 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, as in BINDOCLAV, 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**)

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

Amoxicillin, as in BINDOCLAV may be removed from the circulation by haemodialysis. The molecular weight, degree of protein binding and pharmacokinetic profile of clavulanic acid together with information from a single patient with renal insufficiency all suggest that this compound may also be removed by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.2 Penicillins

Pharmacotherapeutic groups: Combinations of penicillins, including beta-lactamase inhibitors.

ATC code: J01CR02

BINDOCLAV is a combination of amoxicillin and clavulanic acid.

Amoxicillin is a semisynthetic beta-lactamase-susceptible penicillin, which has *in vitro* bactericidal activity against a broad spectrum of non-beta-lactamase-producing Gram-positive, and Gram-negative organisms. The spectrum of activity does not include those organisms that produce beta-lactamases, namely resistant staphylococci, and all strains of *Pseudomonas, Klebsiella* and *Enterobacter.*

Clavulanic acid has been shown *in vitro* to be an irreversible inhibitor of beta-lactamases produced by: *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Proteus vulgaris, Haemophilus influenzae, Neisseria gonorrhoea* and *Bacteroides fragilis.* Clavulanic acid does not inactivate the chromosomally mediated (Sykes Type 1 Cephalosporinase) beta-lactamases produced by *Acinetobacter* species, *Citrobacter* species, *Enterobacter,* Indole positive *Proteus, Providencia* species and *Serratia marcescens. In vitro* the formulation showed synergism against amoxicillin-resistant organisms, with no evidence of antagonism and the activity was not reduced in the presence of serum. *(In vitro* activity does not necessarily imply *in vivo* efficacy.) The clavulanic acid component has very little bactericidal action. It does however, by inactivation of susceptible β-lactamases, protect amoxicillin from degradation by a large number of β-lactamase enzymes produced by penicillin-resistant strains of organisms.

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.

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.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin is stable in the presence of acidic gastric secretions. Peak blood levels are achieved 1 – 2 hours after administration. There is a linear dose response in peak serum levels. The pharmacokinetics of amoxicillin and clavulanic acid are closely allied, and neither is adversely affected by the presence of food in the stomach. Both components are rapidly and well absorbed by the oral route of administration. Following oral administration, amoxicillin and clavulanic acid are approximately 70 % bioavailable.

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

Approximately 18 % of the total plasma amoxicillin content and about 25 % of total plasma clavulanic acid content is protein bound. The apparent volume of distribution is around 0,3 – 0,4 L/kg for amoxicillin and around 0,2 L /kg for clavulanic acid. Amoxicillin diffuses readily into most body tissues with the exception of the brain and spinal fluid. Inflammation generally increases the permeability of the meninges to penicillins, and this may apply to amoxicillin.

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 and eliminated in urine and faeces and as carbon dioxide in expired air.

Elimination

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

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 hours after administration of single BINDOCLAV 250 mg/125 mg or 500 mg/125 mg tablets. 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 active ingredient is excreted during the first 2 hours after administration.

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. Since 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

Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increase in patients with renal failure. The total serum clearance of amoxicillin/clavulanic acid decreases proportionately with decreasing renal function. The reduction in serum 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:

Colloidal silicon dioxide

Magnesium stearate

Microcrystalline cellulose

Sodium starch glycolate.

Coating:

Isopropyl alcohol

Methylene chloride

Opadry white (which consists of hypromellose 5cP, hypromellose 15cP, macrogol and titanium dioxide (E171)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 30 °C.

6.4 Special precautions for storage

Do not remove blister strip from carton until required for use.

6.5 Nature and contents of container

BINDOCLAV 375 mg:

Tablets are packed in 25-micron polyamide / 45-micron aluminium foil / 60-micron PVC film (width 138 mm) as the forming material and 25 micron printed aluminium foil (width 138 mm) as the lidding material.

Each blister strip contains 5 tablets.

Pack size: 15's: Each carton contains 3 blister strips of 5 tablets each.

Pack size: 100's: Each carton contains 20 blister strips of 5 tablets each.

BINDOCLAV 625 mg:

Tablets are packed in 25-micron polyamide / 45-micron aluminium foil / 60-micron PVC film (width 138 mm) as the forming material and 25-micron printed aluminium foil (width 138 mm) as the lidding material.

Each blister strip contains 5 tablets.

Pack size: 15's: Each carton contains 3 blister strips of 5 tablets each.

BINDOCLAV 1 000 mg:

- Tablets are packed in 25-micron polyamide / 45-micron aluminium foil / 60-micron PVC film

(width 138 mm) as the forming material and 25-micron printed aluminium foil (width 138 mm) as the lidding material.

Each blister strip contains 5 tablets.

Pack size: 10's: Each carton contains 2 blister strips of 5 tablets each.

- Tablets are packed in printed 40-micron aluminium foil laminated with 150-gauge poly on one side and plain 40-micron aluminium foil laminated with 150-gauge poly on other side. Each blister strip contains 10 tablets.

  Pack size: 10's: One blister strip pack containing tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

CIPLA MEDPRO (PTY) LTD.

Building 9, Parc du Cap

Mispel Street,

Bellville,

7530

Customer care: 080 222 6662

8. REGISTRATION NUMBERS

BINDOCLAV 375 mg: 41/20.1.2/0532

BINDOCLAV 625 mg: 41/20.1.2/0533

BINDOCLAV 1 000 mg: 41/20.1.2/0534

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 August 2008

10. DATE OF REVISION OF THE TEXT

12 May 2025