# PROFESSIONAL INFORMATION (CLEAN)

## SCHEDULING STATUS

S4

## PROPRIETARY NAME AND DOSAGE FORM

**BINDOCLAV SUSPENSION 125-31.25 mg/5 ml** (Powder for oral suspension)

**BINDOCLAV SUSPENSION 250-62.5 mg/5 ml** (Powder for oral suspension)

## COMPOSITION

**BINDOCLAV SUSPENSION 125-31.25 mg/5 ml:**

Each 5 ml (after reconstitution) contains: amoxicillin trihydrate Ph.Eur, equivalent to amoxicillin 125 mg and potassium clavulanate Ph.Eur. equivalent to clavulanic acid 31,25 mg.

**BINDOCLAV SUSPENSION 250-62.5 mg/5 ml:**

Each 5 ml (after reconstitution) contains: amoxicillin trihydrate Ph.Eur. equivalent to amoxicillin 250 mg and potassium clavulanate Ph.Eur. equivalent to clavulanic acid 62,5 mg.

Sugar-free.

The other ingredients of the formulation are colloidal anhydrous silica, succinic acid, hypromellose, xanthan gum, strawberry guarana flavor, aspartame and silicon dioxide.

## PHARMACOLOGICAL CLASSIFICATION

A 20.1.2 Penicillins

## PHARMACOLOGICAL ACTION

**Pharmacodynamic properties:**

**BINDOCLAV SUSPENSION** 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. 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.
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.)

Resistant organisms include:

*Staphylococcus aureus, Enterococcus faecium, Klebsiella pneumoniae, Acinetobacter baumanii, Staphylococcus epidermidis.*

Pharmacokinetic properties

Absorption:

The two components of Bindoclav, amoxicillin and clavulanic acid are fully dissociated in aqueous solution at physiological pH. Both components are well absorbed by the oral route of administration. Absorption of amoxicillin-clavulanic acid isopitimised when taken at the start of a meal.

Distribution

Amoxicillin and clavulanic acid diffuse readily into most body tissues and fluids with the exception of the brain and spinal fluid. Neither amoxicillin nor clavulanic acid is highly protein bound, clavulanic acid is found to be approximately 25 % bound to human serum and amoxicillin approximately 18 % bound.

Elimination

The major route of elimination for amoxicillin is the kidneys, whereas for clavulanic acid it is by both renal and non-renal mechanisms. Approximately 60-70 % of amoxicillin and 40-65 % clavulanic acid is excreted unchanged in urine during the first 6 hours after administration.

Amoxicillin is also partly excreted in the urine as the inactive metabolite (penicilloic acid) in quantities equivalent to 10-25 % of the initial dose. Clavulanic acid is extensively metabolised and the metabolites are eliminated in urine and faeces and as $CO_2$ in expired air.

**INDICATIONS**

**BINDOCLAV SUSPENSION** 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 SUSPENSION** 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.

In the treatment of infections caused by *Pseudomonas aeruginosa*, an aminoglycoside should be administered concomitantly.

**CONTRA-INDICATIONS**

Hypersensitivity to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented.

**BINDOCLAV SUSPENSION** is contra-indicated in patients with a previous history of amoxicillin/clavulanic-associated jaundice/hepatic dysfunction.

Safety in children under 2 months of age has not been established.

**WARNINGS AND SPECIAL PRECAUTIONS**

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy. Before initiating therapy with **BINDOCLAV SUSPENSION**, 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.

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

Prolonged use may result in overgrowth of non-susceptible organisms. Pseudomembranous enterocolitis has been reported and clostridium difficile associated diarrhea (CDAD) have been reported with amoxicillin contained in **BINDOCLAV SUSPENSION.** It may range in severity from

mild to life threatening. Therefore it is important to consider this is patients who present with diarrhea during or subsequent to the administration of **BINDOCLAV SUSPENSION.**

Prolongation of prothrombin time has been reported in patients receiving **BINDOCLAV SUSPENSION**.

Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

Dose adjustment of the oral anticoagulants such as warfarin maybe necessary.

Transient hepatitis and cholestatic jaundice has been reported.

Changes in liver function tests have been observed in some patients receiving **AUROXILSUSPENSION.** It should be used with care in patients with evidence of severe hepatic dysfunction.

The events may be severe, and occur predominantly in adult 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 raise in aspartate transaminase (AST) and/or alanine transaminase (ALT) has been noted in patients treated with amoxicillin/ clavulanic acid such as in **BINDOCLAV SUSPENSION**.

**BINDOCLAV SUSPENSION** should be used with caution in patients with evidence of hepatic dysfunction.

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

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

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

**BINDOCLAV SUSPENSION** 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.

Since **BINDOCLAV SUSPENSION** 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. **BINDOCLAV SUSPENSION** should be given with caution to patients with lymphatic leukemia since they are especially susceptible to amoxicillin induced skin rashes.

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.

**Impaired hepatic function**:

Changes in liver function tests have been observed in some patients receiving **BINDOCLAV SUSPENSION**. It should be used with care in patients with evidence of severe hepatic dysfunction.

**Impaired renal function:**

In patients with moderate or severe renal impairment **BINDOCLAV SUSPENSION** dosage should be adjusted.

(See **DOSAGE AND DIRECTIONS FOR USE**).

The use of **BINDOCLAV SUSPENSION** 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.

**Effects on ability to drive and use machines**

The use of **BINDOCLAV SUSPENSION** may cause dizziness. Caution must be exercised whilst driving or operating machinery.

**BINDOCLAV SUSPENSION** contains aspartame and should be used with caution in patients with phenylketonuria.

**INTERACTIONS**

**BINDOCLAV SUSPENSION** may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

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

Co-administration of probenecid has little effect on the clavulanic acid component of **BINDOCLAV SUSPENSION**, but delays amoxicillin excretion

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

No information is available about the concurrent use of **BINDOCLAV SUSPENSION** and alcohol. However, the indigestion of alcohol whilst being treated with some other β-lactam antibiotics has precipitated in disulfiram (Antabuse) like reaction in some patients. Therefore, the ingestion of alcohol should be avoided during and for several days after treatment with **BINDOCLAV SUSPENSION.**

There have been reports of increased prothrombin time in patients receiving **BINDOCLAV SUSPENSION** and anticoagulant therapy concomitantly.

**Interaction with Laboratory tests:**

It is recommended that when testing for the presence of glucose in urine during **BINDOCLAV SUSPENSION** treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

**PREGNANCY AND LACTATION**

**Use in Pregnancy:**

The safety of **BINDOCLAV SUSPENSION** in pregnancy has not been established. There is limited information on the use of **BINDOCLAV SUSPENSION** in pregnancy and its use should be avoided in pregnancy, unless considered essential by the-medical practitioner.

In woman with pre-term, premature rupture of the foetal membrane (pPROM) prophylactic treatment with amoxicillin-clavulanate maybe associated with an increased risk of necrotising enterocolitis in neonates

**Use in Lactation:**

Amoxicillin is distributed into breast milk. The use of **BINDOCLAV SUSPENSION** by mothers breast feeding their infants may lead to sensitisation, diarrhoea, candidiasis and skin rash in the infant. Mothers who are treated with **BINDOCLAV SUSPENSION** should not breastfeed their infants.

**DOSAGE AND DIRECTIONS FOR USE**

**Directions for reconstitution:**

**BINDOCLAV SUSPENSION 125-31.25 mg/5 ml:**

For reconstitution to 100 ml, add 92 ml water, invert the bottle and shake well until all the powder is dispersed.

**BINDOCLAV SUSPENSION 250-62.5 mg/5 ml:**

For reconstitution to 100 ml, add 90 ml water, invert the bottle and shake well until all the powder is dispersed.

**BINDOCLAV SUSPENSION** should be taken immediately before a meal.

Dosage:

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.

Children 2-12 years:

The dose of **BINDOCLAV SUSPENSION** 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.

Children weighing 40Kg and over should be dosed according to adult recommendations.

Dosage Guide:

**Amoxicillin-Sensitive Organisms**

| Product | Upper Respiratory Tract Infections | Lower Respiratory Tract Infections | Urinary Tract Infections | Skin & Soft Tissue Infections |
|---|---|---|---|---|
| **BINDOCLAV SUSPENSION 125-31.25 mg/5 ml (13-21 kg) (2-6 years)** | 5-10 ml * 8 hourly | 5-10 ml * 8 hourly | 5-10 ml * 8 hourly | 5-10 ml * 8 hourly |
| **BINDOCLAV SUSPENSION 250-62.5 mg/5 ml (22-40 kg) (7-12 years)** | 5 ml * 8 hourly | 5 ml * 8 hourly | 5 ml * 8 hourly | 5 ml * 8 hourly |

**Amoxicillin-Resistant Organisms**

| Product | Upper Respiratory Tract Infections (Otitis media) | Lower Respiratory Tract Infections (Bronchitis) | Urinary Tract Infections | Skin & Soft Tissue Infections |
|---|---|---|---|---|
| **BINDOCLAV SUSPENSION 125-31.25 mg/5 ml (13-21 kg) (2-6 years)** | 5-10 ml ^ 8 hourly | 5-10 ml * 8 hourly | 5-10 ml * 8 hourly | 5-10 ml * 8 hourly |
| **BINDOCLAV SUSPENSION 250-62.5 mg/5 ml (22-40 kg) (7-12 years)** | 5-10 ml ^ 8 hourly | 5-10 ml * 8 hourly | 5-10 ml * 8 hourly | 5-10 ml * 8 hourly |

* To correspond to a dosage of 25-50 mg/kg/day.

^ To correspond to a dosage of 50 mg/kg/day.

Children aged 2 months to 2 years:

Children under 2 years should be dosed according to body weight.

Safety in children under 2 months of age has not been established (see **Contra-Indications**)

**Impaired renal function**

Both amoxicillin and clavulanic acid are excreted by the kidney and the serum half-line of each, but particularly of amoxicillin, increases in patients with renal failure. Therefore, the dose may need to be reduced or the dosing interval extended. Dosage adjustments are based on the maximum recommended level of amoxicillin.

| Mild impairment | Moderate impairment | Severe impairment |
|---|---|---|
| Creatinine clearance greater than 30 ml/minute. | Creatinine clearance 10 to 30 ml/minute. | Creatinine clearance less than 10 ml/minute. |
| No change in dosage | 15/3,75 mg/kg given 12 hourly. | 15/3,75 mg/kg given as a single dose. |
| | Maximum amoxicillin dose: 30 mg/kg/day. | Maximum amoxicillin dose: 15 mg/kg/day. |

**SIDE EFFECTS**

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

**Infections and infestations:**

*Frequent:* Mucocutaneous candidiasis (including vaginitis)

**Blood and lymphatic system disorders:**

*Less frequent:* Reversible leukopenia (including neutropenia) and thrombocytopenia, reversible agranulocytosis, haemolytic anaemia, prolongation of bleeding time and prothrombin time (see **WARNINGS AND SPECIAL PRECAUTIONS**).

**Immune system disorders:**

*Less frequent:* Serum sickness-like syndrome. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see **WARNINGS AND SPECIAL PRECAUTIONS**).

Hypersensitivity vasculitis.

**Nervous system disorders:**

*Less frequent:* Dizziness, headache, reversible hyperactivity and convulsions. Convulsions may occur in patients with impaired renal function or in those receiving high doses.

**Gastrointestinal disorders:**

*Frequent:* Nausea, vomiting, diarrhoea

*Less frequent:* Glossitis

*The following side effects have been reported and frequencies are unknown:*

Indigestion, abdominal pain, gastritis, stomatitis, black 'hairy' tongue, enterocolitis, mucocutaneous candidiasis and antibiotic-associated colitis (including pseudomembranous colitis, Clostridium difficile associated diarrhoea (CDAD) and haemorrhagic colitis) and abnormal taste. Superficial tooth discolouration especially with the suspension formulations. It can usually be removed by brushing.

If gastrointestinal reactions are evident, they may be reduced by taking **BINDOCLAV SUSPENSION** at the start of a meal.

**Hepato-biliary disorders:**

*Less frequent:* Hepatitis and cholestatic jaundice.

**Skin and subcutaneous tissue disorders:**

*Less frequent:* Skin rash, pruritus, urticarial, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis, acute generalised exanthematous pustulosis (AGEP).

If any hypersensitivity dermatitis reaction occurs, treatment should be discontinued

**Renal and urinary disorders:**

*The following side effects have been reported and frequencies are unknown:*

Crystalluria, interstitial nephritis.

**Reproductive system and breast disorders:**

*The following side effects have been reported and frequencies are unknown:*

Vaginitis.

**KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT**

Overdosage with amoxicillin 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 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.

## IDENTIFICATION

**BINDOCLAV SUSPENSION 125-31.25 mg/5 ml:**

White to off white granular powder forming a white to off white suspension with a strawberry flavour on constitution with water.

**BINDOCLAV SUSPENSION 250-62.5 mg/5 ml:**

White to off white granular powder forming a white to off white suspension with a strawberry flavour on constitution with water.

## PRESENTATION

**BINDOCLAV SUSPENSION 125-31.25 mg/5 ml:**

One 150 ml heavy weight HDPE translucent, round bottle closed with a screw cap packed in a printed carton with a package insert.

(100 ml of suspension after reconstitution)

One 200 ml Amber coloured, round glass bottle closed with a screw cap packed in a printed carton with a package insert.

(100 ml of solution after reconstitution).

**BINDOCLAV SUSPENSION 250-62.5 mg/5 ml:**

One 150 ml heavy weight HDPE translucent, white opaque round bottle closed with a screw cap packed in a printed carton with a package insert.

(100 ml of suspension after reconstitution).

One 200 ml Amber coloured, round glass bottle closed with a screw cap packed in a printed carton with a package insert.

(100 ml of solution after reconstitution)

## STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from moisture.

STORAGE FOR RECONSTITUTED SUSPENSION:

Reconstituted Suspension should be kept in a refrigerator (2 – 8 °C) and used within 7 days. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

## REGISTRATION NUMBER

**BINDOCLAV SUSPENSION 125-31.25 mg/5 ml:** 41/20.1.2/0965

**BINDOCLAV SUSPENSION 250-62.5 mg/5 ml:** 41/20.1.2/0966

## NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

**Aurogen South Africa (Pty) Ltd**

**Woodhill Office Park, Building 1,**

53 Phillip Engelbrecht Avenue,

Meyersdal, Ext. 12,

1448,

Johannesburg,

South Africa

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