Applicant/PHCR: Unicorn Pharmaceuticals (Pty) Ltd
Product proprietary name: Betaclav 1000
Dosage form: Each Tablet contains Amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.
Date of submission: July 2016

PACKAGE INSERT

SCHEDULING STATUS: S4

PROPRIETARY NAMES and dosage form

BETACLAV 375 tablets

BETACLAV 625 tablets

BETACLAV 1 000 tablets

COMPOSITION

Betaclav 375: Each tablet contains amoxicillin trihydrate equivalent to amoxicillin 250 mg and potassium clavulanate equivalent to clavulanic acid 125 mg.

Betaclav 625: Each tablet contains amoxicillin trihydrate equivalent to amoxicillin 500 mg and potassium clavulanate equivalent to clavulanic acid 125 mg.

Betaclav 1 000: Each tablet contains amoxicillin trihydrate equivalent to amoxicillin 875 mg and potassium clavulanate equivalent to clavulanic acid 125 mg.
Sugar free.

PHARMACOLOGICAL CLASSIFICATION: A 20.1.2 Penicillins

PHARMACOLOGICAL ACTION

Betaclav 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 gonorrhoeae* 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.

Pharmacokinetics

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.

Distribution

Approximately 18% of the total plasma amoxicillin content is protein bound. 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.

Excretion

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. Small amounts of amoxicillin are also excreted in the faeces and bile.

INDICATIONS

Betaclav 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.

Betaclav 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.

CONTRA-INDICATIONS

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

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

WARNINGS

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

Betaclav 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.

Prolonged use may result in overgrowth of non-susceptible organisms.

Pseudomembranous enterocolitis has been reported.

Prolongation of prothrombin time has been reported rarely in patients receiving **Betaclav**. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

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

Transient hepatitis and cholestatic jaundice has been reported. **Betaclav** should be used with caution in patients with evidence of hepatic dysfunction.

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

INTERACTIONS

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

Betaclav may reduce the efficacy of oral contraceptives and patients should be warned accordingly.

The concomitant administration of allopurinol and ampicillin 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.

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

Interaction with laboratory tests

It is recommended that when testing for the presence of glucose in urine during **Betaclav** 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 **Betaclav** in pregnancy has not been established.

Use in lactation

Amoxicillin is 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.

DOSAGE AND DIRECTIONS FOR USE:

Tablets should be taken immediately before a meal.

Dosages

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 for **Betaclav** is one **Betaclav 375** 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 **Betaclav 625** tablet every eight hours at the start of a meal, or one **Betaclav 1 000** tablet every 12 hours at the start of a meal. Since **Betaclav 375, 625 and 1 000** tablets contain the same amount of clavulanic acid (125 mg as the potassium salt), two **Betaclav 375** tablets are not equivalent to one **Betaclav 625** tablet, and two **Betaclav 625** tablets are not equivalent to one **Betaclav 1 000**. Therefore, two **Betaclav 375** tablets

should not be substituted for one **Betaclav 625** tablet or two **Betaclav 625** tablets for one **Betaclav 1 000** tablet for the treatment of more severe infections.

Impaired renal function

Both amoxicillin and clavulanic acid are excreted by the kidneys and the serum half-life of each increases in patients with renal failure. Therefore, 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:

Betaclav 375, 625

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 twelve hours.

Betaclav 1 000 should not be used in patients with a 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.

Dosage Guide

Amoxicillin-Sensitive Organisms

Product	**Upper Respiratory Tract Infections**	**Lower Respiratory Tract Infections**	**Urinary Tract Infections**	**Skin & Soft Tissue Infections**
Betaclav 375	1 tablet 8 hourly	-	1 tablet 8 hourly	1 tablet 8 hourly
Betaclav 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
Betaclav 1 000	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly

Amoxicillin-Resistant Organisms

Product	Upper Respiratory Tract Infections (otitis media)	Lower Respiratory Tract Infections (bronchitis)	Urinary Tract Infections	Skin & Soft Tissue Infections
Betaclav 375	-	-	1 tablet 8 hourly	1 tablet 8 hourly
Betaclav 625	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly	1 tablet 8 hourly
Betaclav 1 000	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly	1 tablet 12 hourly

SIDE-EFFECTS AND SPECIAL PRECAUTIONS

Side-effects

The most frequently reported adverse effects are diarrhoea, nausea, vomiting, indigestion, abdominal pain, skin rashes, urticaria and erythema multiforme, vaginitis, 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 **Betaclav** at the start of a meal. In

addition, as these symptoms are especially related to the potassium clavulanate component, where these gastro-intestinal 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 **Betaclav:**

Blood and lymphatic system disorders

Rare (> 1/10 000 ≤ 1/1 000): Reversible leucopenia and reversible thrombocytopenia.

Very rare (≤ 1/10 000): Haemolytic anaemia, agranulocytosis, prolongation of bleeding time and prothrombin time. Appropriate monitoring should be undertaken when anticoagulants are prescribed concomitantly.

The following side effects have been reported and frequencies are unknown: Thrombocytopenic purpura, eosinophilia.

These reactions are usually reversible on discontinuation of therapy and are believed to be hypersensitivity phenomena. A slight thrombocytosis was noted in less than 1% of the patients treated with **Betaclav**.

Immune system disorders

Very rare (≤ 1/10 000): Serum sickness-like syndrome, hypersensitivity vasculitis. Whenever such reactions occur, **Betaclav** should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see **Warnings**).

Nervous system disorders

Uncommon (> 1/1 000 ≤ 1/100): Dizziness, headache.

Very rare (≤ 1/10 000): Reversible hyperactivity, convulsions. Convulsions may occur with impaired renal function or in those receiving high doses.

Gastro-intestinal disorders

Common (> 1/100 ≤ 1/10): Diarrhoea, nausea, vomiting, mucocutaneous candidiasis (including vaginitis).

Uncommon (> 1/1 000 ≤ 1/100): Indigestion.

Very rare (≤ 1/10 000): Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), superficial tooth discolouration has been reported, especially with the suspension and chewable tablet formulations. It can usually be removed by brushing.

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

Abdominal pain, abnormal taste, gastritis, stomatitis, glossitis, black 'hairy' tongue, enterocolitis.

If gastro-intestinal reactions are evident, they may be reduced by taking **BETACLAV** at the start of a meal.

Hepatobiliary disorders

Uncommon (> 1/1 000 ≤ 1/100): A moderate rise in aspartate transaminase (AST) and/or alanine transaminase (ALT) has been noted in patients treated with **Betaclav**, but the significance of these findings is unknown.

Very rare (≤ 1/10 000): Hepatitis and cholestatic jaundice have been reported. 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.

Skin and subcutaneous tissue disorders

Uncommon (> 1/1 000 ≤ 1/100): Skin rashes, pruritus, urticaria.

Rare (> 1/10 000 ≤ 1/1 000): Erythema multiforme.

Very rare (≤ 1/10 000): Stevens-Johnson syndrome, toxic epidermal necrolysis, bullous exfoliative dermatitis.

Whenever such reactions occur, **Betaclav** should be discontinued.

Renal effects

Very rare (≤ 1/10 000): Interstitial nephritis, crystalluria.

General disorders

The following have been reported and frequencies are unknown: Tiredness, hot flushes.

Special Precautions

Caution is needed when administering amoxicillin 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.

The sodium content must be taken into account in patients on a sodium-restricted diet if the administration of high doses is necessary.

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

Since **Betaclav** 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. **Betaclav** should be given with caution to patients with lymphatic leukaemia 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 **Betaclav.** 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 **Betaclav** dosage should be adjusted (see **Dosage and Directions for use**).

Use in lactation

Amoxicillin is excreted in the milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when **Betaclav** is administered to a nursing woman.

The use of **Betaclav** 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.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

Overdosage with amoxicillin is usually asymptomatic. However, gastro-intestinal 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 the compound may also be removed by haemodialysis.

IDENTIFICATION

Betaclav 375

White, oval shaped film-coated tablets, debossed with "A" on one side and "63" on the other side.

Betaclav 625

White, oval shaped film-coated tablets, debossed with "A" on one side and "64" on the other side.

Betaclav 1 000

White, 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.

PRESENTATION

Betaclav 375

Blister packs composed of silver coloured cold form laminate (polyamide/aluminium foil/PVC film) as the forming material and silver coloured aluminium foil as the lidding material. Cartons contain 15's (3 x 5) or 100's (20 x 5) tablets.

Betaclav 625

Blister packs composed of silver coloured cold form laminate (polyamide/aluminium foil/PVC film) as the forming material and silver coloured aluminium foil as the lidding material. Cartons contain 15's (3 x 5) tablets.

Betaclav 1 000

Carton containing 10 tablets of a single strip pack composed of silver coloured laminated aluminium/aluminium foil.

Blister packs composed of silver coloured cold form laminate (polyamide/aluminium foil/PVC film) as the forming material and silver coloured aluminium foil as the lidding material. Cartons contain 10's (2 x 5) tablets.

STORAGE INSTRUCTIONS

Store at or below 30 °C. Protect from light and moisture. Keep the blisters in the carton until required for use.

Applicant/PHCR: Unicorn Pharmaceuticals (Pty) Ltd
Product proprietary name: Betaclav 1000
Dosage form: Each Tablet contains Amoxicillin trihydrate equivalent to 875 mg amoxicillin and potassium clavulanate equivalent to 125 mg clavulanic acid.
Date of submission: July 2016

KEEP THIS MEDICINE OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

Betaclav 375: 41/20.1.2/0546

Betaclav 625: 41/20.1.2/0547

Betaclav 1 000: 41/20.1.2/0548

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

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DATE OF PUBLICATION OF THE PACKAGE INSERT

The date on the registration certificate of the medicine: 15 August 2008

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CODE: IBETCL