**PROFESSIONAL INFORMATION**

**SCHEDULING STATUS: S4**

## 1. NAME OF THE MEDICINE

**RANCLAV 1 g** Film-coated tablets

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains

Amoxicillin trihydrate

equivalent to amoxicillin 875 mg

Clavulanate potassium

equivalent to clavulanic acid 125 mg

Sugar free

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

*Film-coated tablets*

White, film-coated, capsule shaped tablets debossed with ‘RX509’ on one side and a scoreline on the other.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

**RANCLAV 1 g** is 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.

**RANCLAV 1 g** 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 in order to prevent any possibility of amoxicillin crystalluria.

***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**

For severe infections and infection of the respiratory tract, the adult dose for **RANCLAV 1 g** is one **RANCLAV 1 g** tablet every 12 hours at the start of a meal.

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

**Special populations**

***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.

**RANCLAV 1 g** should not be used in patients with a glomerular filtration rate of <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 Infection** | **Lower Respiratory Tract Infection** | **Urinary Tract Infection** | **Skin & Soft Tissue Infections** |
| **Adults:** | | | | |
| **RANCLAV 1 g** | 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)** ***H. influenzae, H. parainfluenzae*** | **Lower Respiratory Tract Infection (bronchitis)** ***H. influenzae, H. parainfluenzae*** | **Urinary Tract Infection** ***E. coli, Klebsiella pneumoniae*** | **Skin & Soft Tissue Infections** ***Staphylo-coccus aureus*** |
| **Adults:** | | | | |
| **Ranclav 1 g** | 1 tablet 12 hourly | 1 tablet 12 hourly | 1 tablet 12 hourly | 1 tablet 12 hourly |

**Paediatric population**

Other pharmaceutical forms/strengths may be more appropriate for administration to this population.

**Method of administration**

Oral use.

Tablets should be taken immediately before a meal.

**4.3 CONTRAINDICATIONS**

Hypersensitivity to penicillins and cephalosporins or to any of the excipients listed in Section 6.1. Cross-sensitivity between penicillins and cephalosporins is well documented.

**RANCLAV 1 g** is contraindicated in patients with a previous history of amoxicillin/clavulanic acid associated jaundice/hepatic dysfunction.

**4.4 Special warnings and precautions for use**

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions 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).

Before initiating therapy with **RANCLAV 1 g**, 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 a hypersensitivity reaction occurs, **RANCLAV 1 g** 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.

Since **RANCLAV 1 g** 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.

**RANCLAV 1 g** should be avoided if infectious mononucleosis is suspected.

**RANCLAV 1 g** should be given with caution to patients with lymphatic leukaemia since they are especially susceptible to amoxicillin induced skin rashes.

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

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.

Prolongation of prothrombin time has been reported rarely in patients receiving **RANCLAV 1 g**. Appropriate monitoring should be undertaken when anticoagulants are prescribed concurrently.

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

**Impaired hepatic function**

Changes in liver function tests have been observed in some patients receiving **RANCLAV 1 g**.

Transient hepatitis and cholestatic jaundice has been reported. **RANCLAV 1 g** should be used with caution in patients with evidence of hepatic dysfunction.

**Impaired renal function**

In patients with moderate or severe renal impairment **RANCLAV 1 g** dosage should be adjusted (See section 4.2).

**RANCLAV 1 g** should not be used in patients with a glomerular filtration rate of less than 30 mL/minute.

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

In patients with reduced urine output, crystalluria (including acute renal injury) has been observed very rarely, predominantly with parenteral therapy.

During the administration of high doses of amoxiciliin, 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

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

The use of **RANCLAV 1 g** 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

Drug-induced enterocolitis syndrome (DIES) has been reported mainly in children receiving amoxicillin/clavulanate (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.

**4.5 Interaction with other medicines and other forms of interaction**

Concomittant use of Probenecid is not recommended. Probenecid decreases the renal tubular secretion of amoxicillin but does not affect clavulanic acid excretion. Concurrent use of probencid with RANCLAV 1 g may result in increased and prolonged blood levels of amoxicillin, but not of clavulanic acid.

RANCLAV 1 g 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 medicines may interfere with the bactericidal effects of amoxicillin.

Methotrexate

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

**Interaction with laboratory tests**

It is recommended that when testing for the presence of glucose in urine during RANCLAV 1 g treatment, enzymatic glucose oxidase methods should be used. Due to the high urinary concentrations of amoxicillin, false positive readings are common with chemical methods.

**4.6 Fertility, pregnancy and lactation**

**Pregnancy**

The safety of **RANCLAV 1 g** in pregnancy has not been established.

**Lactation**

Amoxicillin is distributed in 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.

Amoxicillin is excreted in breast milk; there are no data on the excretion of clavulanic acid in human milk. Therefore, caution should be exercised when **RANCLAV 1 g** is administered to a nursing woman.

**Fertility**

There is no fertility data available.

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

Patients should be made aware of the symptoms of dizziness or convulsions (when high doses are used), and should be careful when driving, or operating machinery.

**4.8 Undesirable effects**

**a. Summary of the safety profile**

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 **RANCLAV 1 g** 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 amoxicillin separately.

**b. Tabulated list of adverse reactions**

| **MedDRA System organ class** | **Frequency** | **Adverse reactions** |
|---|---|---|
| *Infections and Infestations* | Frequent | Vaginitis |
| | Frequency Unknown | Mucocutaneous candidiasis. |
| *Blood and lymphatic system disorders* | Less Frequent | Prolongation of bleeding time and prothrombin time; thrombosis |
| | Frequency Unknown | Haemolytic anaemia, reversible thrombocytopenia, thrombocytopenic purpura, eosinophilia, reversible leucopenia and agranulocytosis. |
| These reactions are usually reversible on discontinuation of therapy and are believed to be | | |

| | | |
|---|---|---|
| hypersensitivity phenomena | | |
| *Immune system disorders* | Frequency Unknown | Angioneurotic oedema, anaphylaxis, serum sickness-like syndrome, hypersensitivity vasculitis. |
| Whenever such reactions occur, **RANCLAV 1 g** should be discontinued.<br>Serious and occasional fatal hypersensitivity (anaphylactic) reactions and angioneurotic oedema can occur with oral penicillin (see section 4.4). | | |
| *Nervous system disorders* | Frequent | Headache, dizziness, hot flushes |
| | Less Frequent | Reversible hyperactivity, convulsions. |
| | Unknown | Asceptic meningitis |
| Convulsions may occur with impaired renal function or in those receiving high doses. | | |
| *Gastrointestinal disorders* | Frequent | Diarrhoea, nausea, vomiting, indigestion, abdominal pain |
| | Frequency Unknown | Antibiotic-associated colitis (including pseudomembranous colitis and haemorrhagic colitis), black hairy tongue, gastritis, stomatitis, glossitis. Drug-induced enterocolitis syndrome, pancreatitis acute (DIES) |
| If gastro-intestinal reactions are evident, they may be reduced by taking **RANCLAV 1 g** at the start of a meal. | | |
| *Hepato-biliary disorders* | Frequency Unknown | Hepatitis*, cholestatic jaundice*.<br>Rises in AST and/or ALT. |
| *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 events 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* | Frequent | Skin rashes, urticaria, pruritus and erythema multiforme |
| | Less Frequent | Stevens-Johnson syndrome, Toxic epidermal necrolysis, Bullous exfoliative-dermatitis |
| | Unknown | Linear IgA disease |
| Whenever such reactions occur, **RANCLAV 1 g** should be discontinued. | | |
| *Renal and urinary disorders* | Frequency Unknown | Interstitial nephritis, Crystalluria (including acute renal injury) |
| *General disorders and administration site conditions* | Frequent | Abnormal taste; tiredness |
| *Cardiac disorders* | Unknown | Kounis syndrome |

*Reporting of suspected adverse reactions*

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.

**4.9 Overdose**

**Symptoms and signs**

Overdosage with amoxicillin is usually asymptomatic. However, gastro-intestinal effects such as nausea, vomiting and diarrhoea may be evident.

Amoxicillin crystalluria, in some cases leading to renal failure, has been observed (see section 4.4).

**Management:**

Symptoms of water and electrolyte imbalance should be treated symptomatically. Adequate fluid intake and urinary output must be maintained to minimize the possibility of crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see sections 4.8 and 4.9).

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.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

A 20.1.2 Penicillins

**RANCLAV 1 g** is a combination of amoxicillin and clavulanic acid.

Amoxicillin is a semi-synthetic 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 which produce beta-lactamases, namely resistant staphylococci and all strains of *Pseudomonas, Klebsiella and Enterobacter*.

Clavulanic acid has been shown 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.

### 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.

*Distribution*

Approximately 18 % of the total 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 penicillin 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.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

*Tablet core:*

Microcrystalline cellulose

Sodium Starch Glycolate

Silica, colloidal anhydrous

Povidone

Basic butylated methacrylate copolymer

Isopropyl Alcohol

Magnesium stearate

*Film-coat*

Opadry 03858965 White

Macrogol/ PEG 400

Isopropyl Alcohol

Methylene Chloride

### 6.2 Incompatibilities

Not applicable.

### 6.3 Shelf life

24 months.

**6.4 Special precautions for storage**

Store below 25 °C in the original package, protected from moisture.

**6.5 Nature and contents of container**

Carton contains 10 tablets packed in a PVC/PVdC blister pack within a 4-layered laminated bag containing a desiccant sachet.

**PVC/PVdC blister pack in a 4-layered laminated bag:**

Clear PVC film coated with PVdC on the inner side with the lidding of hard tempered, aluminium foil coated with heat seal lacquer on the inner side.

One blister to be put into a 4-layered laminated bag containing a desiccant sachet.

The structure of the four layered laminated bag is as follows: Polyester film/ Aluminium foil/ Polyester film/ Polyethylene.

**6.6 Special precautions for disposal**

No special requirements.

**7. HOLDER OF CERTIFICATE OF REGISTRATION**

Ranbaxy Pharmaceuticals (Pty) Ltd
14 Lautre Road, Stormill Ext 1

Roodepoort, 1724

South Africa

**8. REGISTRATION NUMBER:**

A40/20.1.2/0568

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

August 2007

**10. DATE OF REVISION OF THE TEXT**

14 April 2025

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| Namibia: NS2 Reg. no.: 07/20.1.2/0182 |

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| Botswana: S2 Reg. no.: BOT0701095 |