PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RANCLAV 625

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated tablet contains:

Amoxicillin trihydrate equivalent to amoxicillin…500 mg

Potassium clavulanate equivalent to clavulanic acid….125 mg

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RANCLAV 625

White to off-white film coated oval shaped tablets debossed with “RX713” on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RANCLAV 625 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 625 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 does not contribute to the therapeutic effect.

4.2 Posology and method of administration

RANCLAV 625 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.

Adult: The adult dose for **RANCLAV 625** is one tablet every eight hours at the start of a meal.

Dosage guide:

AMOXICILLIN SENSITIVE ORGANISMS

Product	**Upper respiratory tract infections**	**Lower respiratory tract infections**	**Urinary tract infections**	**Skin and soft tissue infections**
ADULTS:				
RANCLAV 625	1 tablet 8-hourly	1 tablet 8-hourly	1 tablet 8-hourly	1 tablet 8-hourly

AMOXICILLIN RESISTANT ORGANISMS

Product	**Upper respiratory tract infections**	**Lower respiratory tract infections**	**Urinary tract infections**	**Skin and soft tissue infections**
	(Otitis media) *H. influenzae, H. parainfluenzae*	(Bronchitis) *H. influenzae, H. parainfluenzae*	*E. coli*, *Klebsiella Pneumoniae*	*Staphylococcus aureus*
ADULTS:				
RANCLAV 625	1 tablet 8-hourly	1 tablet 8-hourly	1 tablet 8-hourly	1 tablet 8-hourly

Special populations

Renal Impairment: Both amoxicillin and clavulanic acid are excreted by 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:

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-twelve hours.

Severe impairment (creatinine clearance less than 10 ml/minute): 1/2 tablet every twelve hours.

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

Paediatric population

No reported data available.

Method of administration

RANCLAV 625 is for oral use.

4.3 Contraindications

- Hypersensitivity to the active substances or to any of the excipients of **RANCLAV 625**.
- Hypersensitivity to penicillins or to cephalosporins. Cross-sensitivity between penicillins and cephalosporins is well documented.
- History of a severe immediate hypersensitivity reaction (e.g. anaphylaxis) to another beta-lactam agent (e.g. carbapenem or monobactam).
- **RANCLAV 625** are contraindicated in patients with a previous history of amoxicillin/clavulanate associated jaundice/hepatic dysfunction (see section 4.8).

4.4 Special warnings and precautions for use

Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients on penicillin therapy.

Before initiating therapy with **RANCLAV 625**, 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, **RANCLAV 625** 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.

RANCLAV 625 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 amoxicillin and clavulanic acid. 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. **RANCLAV 625** should be used with caution in patients with evidence of hepatic dysfunction. Hepatic events have been reported predominantly in males and elderly patients and may be associated with prolonged treatment. 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 medications known to have the potential for hepatic effects (see section 4.8). Changes in liver function tests have been reported in some patients receiving **RANCLAV 625**. It should be used with care in patients with evidence of severe hepatic dysfunction.

Antibiotic-associated colitis has been reported with nearly all antibacterial agents, including **RANCLAV 625**, and may range in severity from mild to life threatening. Therefore, 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, **RANCLAV 625** should immediately be discontinued, a physician be consulted and an appropriate therapy initiated. Anti-peristaltic medicinal products are contra-indicated in this situation.

RANCLAV 625 is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to beta-lactam agents that is not mediated by beta-lactamases susceptible to inhibition by clavulanic acid. This presentation should not be used to treat penicillin-resistant *S. pneumoniae*.

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 4.5). This reaction requires amoxicillin and clavulanic potassium discontinuation and contraindicates any subsequent administration of amoxicillin.

Convulsions may occur in patients with impaired renal function or in those receiving high doses (see section 4.8).
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 in order to reduce the possibility of amoxicillin crystalluria. In patients with bladder catheters, a regular check of patency should be maintained (see section 4.9).

Since **RANCLAV 625** 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. Amoxicillin and clavulanic acid 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.

The presence of clavulanic acid in **RANCLAV 625** may cause a non-specific binding of IgG and albumin by red cell membranes leading to a false positive Coombs test.

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

Impaired renal function:

In patients with moderate or severe renal impairment, amoxicillin and clavulanic acid dosage should be adjusted.

The use of amoxicillin and clavulanic acid 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.

4.5 Interaction with other medicines and other forms of interaction

Probenecid decreases the renal tubular secretion of amoxicillin, but does not affect clavulanic acid excretion. Concurrent use with **RANCLAV 625** may result in increased and prolonged

blood levels of amoxicillin but not of clavulanic acid.

RANCLAV 625 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.

Oral anticoagulants and penicillin antibiotics have been widely used in practice without reports of interaction. However, increased international normalised ratio in patients maintained on acenocoumarol or warfarin and prescribed a course of amoxicillin have been reported. If co-administration is necessary, the prothrombin time or international normalised ratio should be carefully monitored with the addition or withdrawal of amoxicillin. Moreover, adjustments in the dose of oral anticoagulants may be necessary.

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 amoxicillin and clavulanic acid 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 625** in pregnancy has not been established.

Limited data on the use of amoxicillin/clavulanic acid during pregnancy in humans do not indicate an increased risk of congenital malformations. In a single reported study in women with preterm, premature rupture of the foetal membrane it was reported that prophylactic treatment with amoxicillin and clavulanic acid may be associated with an increased risk of necrotising enterocolitis in neonates.

Breastfeeding

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.

Fertility

No fertility data reported.

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 reported. However, undesirable effects may occur (e.g. allergic reactions, dizziness, convulsions), which may influence the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse drug reactions (ADRs) are diarrhoea, nausea and vomiting.

Tabulated summary of adverse reactions

Body System	Frequent	Less Frequent	Frequency Unknown
Infections and Infestations	• Mucocutaneous candidiasis		• Overgrowth of non-susceptible organisms
Blood and the lymphatic system disorders		• Reversible leucopenia (including neutropenia) • Thrombocytopenic	• Reversible agranulocytosis • Haemolytic anaemia • Prolongation of bleeding time and prothrombin time
Immune system disorders			• Angioedema • Anaphylaxis • Serum-sickness-like syndrome • Hypersensitivity vasculitis

Nervous system disorders		• Headache • Dizziness	• Reversible hyperactivity • Convulsions • Aeseptic meningitis
Gastro-intestinal disorders	• Diarrhoea • Nausea[1] • Vomiting • Abnormal taste	• Indigestion	• Antibiotic associated colitis • Black 'hairy' tongue • Gastritis • Stomatitis • Glossitis
Hepatobiliary disorders		• Rises in AST and/or ALT	• Hepatitis • Cholestatic jaundice
Skin and subcutaneous tissue disorders[2]		• Skin rashes • Urticarial • Pruritus • Erythema multiforme	• Stevens-Johnson Syndrome • Toxic epidermal necrolysis • Bullous exfoliative-dermatitis • Acute generalised exanthemous pustulosis (AGEP) • Drug reaction with eosinophilia and systemic symptoms (DRESS)
Renal and urinary disorders			• Interstitial nephritis • Crystalluria
Reproductive system and breast disorders	• Vaginitis • Genital moniliasis		
General disorders			• Superficial tooth

and administrative site conditions			discoloration (can usually be removed by brushing)

[1] Nausea is more often associated with higher oral doses. If gastrointestinal reactions are evident, they may be reduced bt taking amoxicillin/clavlanic acid with a meal.

[2] If any hypersenstitvity dermatitis reaction occurs, treatment should be discontinued.

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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reaction Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage with **RANCLAV 625** 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 minimize 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combinations of penicillins, incl. beta-lactamase inhibitors, ATC code: J01CR02

Mechanism of Action

Bacteriology

Spectrum – **RANCLAV 625** is the group name for formulations containing 2 and 4 parts of a broad spectrum penicillin, amoxicillin and 1 part of potassium clavulanate. Potassium clavulanate 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*. Potassium clavulanate does not inactivate the chromosomally mediated (Sykes Type I 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 organism, 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).

Bactericidal 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.

5.2 Pharmacokinetic properties

Absorption

Amoxicillin and clavulanic acid, are fully dissociated in aqueous solution at physiological pH. Both components are rapidly and well absorbed by the oral route of administration.
Following oral administration, amoxicillin and clavulanic acid are approximately 70 % bioavailable. The plasma profiles of both components are similar and the time to peak plasma concentration (T_{max}) in each case is approximately one hour. The pharmacokinetics of amoxicillin and clavulanic acid are closely allied and neither are adversely affected by the presence of food in the stomach.

Distribution

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 reported 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.
Both amoxicillin and clavulanic acid have been shown to cross the placental barrier (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 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 reported mean elimination half-life of approximately one hour and a mean total clearance of approximately 25 l/h in healthy subjects. The reported urinary excretion for amoxicillin is 50-85 % and between 27-60 % for clavulanic acid over a 24 hour period. Clavulanic acid was reported to be excreted during the first 2 hours after administration. Co-administration of probenecid has little effect on the excretion of the clavulanic acid component of the formulation.

5.3 Preclinical safety data

Non-clinical data reported no special hazard for humans based on studies of safety pharmacology, genotoxicity and toxicity to reproduction.

Repeat dose toxicity studies reported in dogs with amoxicillin/clavulanic acid demonstrate gastric irritancy and vomiting, and discoloured tongue.

Carcinogenicity studies have not been reported with amoxicillin/clavulanic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal anhydrous silica

Eudragit E 100

Isopropyl Alcohol

Magnesium stearate

Methylene chloride

Microcrystalline cellulose

Opadry 03B58965 white

PEG 400

Povidone (K30)

Sodium starch glycolate

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 ºC. Protect from light and moisture.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

PVC/PVdC blister of 10, 15 tablets in a laminated pouch along

with 1 g sachet containing molecular sieve.

6.6 Special precautions for disposal disposal and other handling

Return all unused or expired medicines to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewerage systems (e.g. toilets).

7. HOLDER OF CERTIFICATE REGISTRATION

Ranbaxy Pharmaceuticals (Pty) Ltd

14 Lautre Road

Stormill, Ext. 1, Roodepoort, 1724

South Africa

8. REGISTRATION NUMBER

RANCLAV 625: 50/20.1.1/0227

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 May 2021

10. DATE OF REVISION OF THE TEXT

AMS no.: 5222059