Professional Information

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

CURITAZ™ 4,5 Powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Curitaz™ 4,5 Powder for solution for infusion 100 ml glass bottle contains piperacillin sodium equivalent to piperacillin 4 g and tazobactam sodium equivalent to tazobactam 500 mg.

3. PHARMACEUTICAL FORM

Curitaz™ 4,5 Powder for solution for infusion is a white to yellowish powder.

Ready-for-use solution: Clear colourless to yellowish solution free from fibres and particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CURITAZ is indicated for the treatment of the following systemic and/or local bacterial infections in which susceptible organisms have been detected or are suspected:

Adults:

Bacterial infections in neutropenic patients, in combination with an aminoglycoside.

Community acquired pneumonia caused by *Haemophilus influenzae*.

Intra-abdominal infections caused by piperacillin-resistant β-lactamase producing strains of *Escherichia coli* and *Bacteroides fragilis.*

Gynaecological infections, including endometritis caused by piperacillin-resistant β-lactamase producing strains of *Escherichia coli.*

Skin and soft tissue infections caused by piperacillin-resistant β-lactamase producing strains of *Staphylococcus aureus*.

Children:

Bacterial infections in neutropenic patients, in combination with an aminoglycoside.

Serious intra-abdominal infections, caused by *E. coli* or *Bacteroides* species, in hospitalised children aged 2 to 12 years, (CURITAZ has not been evaluated for this indication in younger children).

Because of its broad spectrum of activity CURITAZ is useful in the treatment of mixed infections and in presumptive therapy before the results of sensitivity tests are known. There is no need to add an additional antibiotic to the treatment of mixed infections caused by piperacillin-sensitive and β-lactamase producing organisms.

4.2 Posology and method of administration

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. Treatment with CURITAZ is recommended for a minimum of 5 days and a maximum of 14 days, but should be continued for 48 hours beyond the resolution of clinical symptoms or the fever. Usual duration of treatment is 7 to 10 days.

Neutropenic patients should be treated with full therapeutic doses of CURITAZ 4plus an aminoglycoside.

Electrolytes should be determined periodically in patients with low potassium reserves because of the possibility of hypokalaemia.

Adults and children over 12 years, with normal renal function:

The usual dosage for adults and children over 12 years is 4, 5 g CURITAZ

(4 g piperacillin/500 mg tazobactam) given every 8 hours.

In immunocompromised and neutropenic patients, the recommended dose is 4,5 g CURITAZ given every 6 hours in combination with an aminoglycoside.

Elderly with normal renal function:

CURITAZ may be used in the same doses as adults except in cases of renal impairment (see below).

Renal insufficiency in adults, the elderly and children over the age of 12 years:

In patients with renal insufficiency, the intravenous dose should be adjusted to the degree of actual renal function impairment. The suggested daily doses are as follows:

Creatinine Clearance (ml/min)	**Recommended CURITAZ dosage**
90 - 40	13,5 g (12 g piperacillin / 1,5 g tazobactam) per day in divided doses of 4,5 g eight hourly or 3,375 g six hourly
20 – 40	9 g per day in divided doses of 2,25 g six hourly
< 20	6,75 g per day in divided doses of 2,25 g eight hourly

For patients on haemodialysis, the maximum daily dose is 2,25 g CURITAZ every eight hours. In addition, because haemodialysis removes 30 to 50 % of piperacillin in 4 hours, one additional dose of 0,75 g CURITAZ should be administered following each dialysis period.
For patients with renal failure and hepatic insufficiency, measurement of serum levels of CURITAZ will provide additional guidance for adjusting dosage.

Children aged 12 years and under with normal renal function:

CURITAZ is only recommended for the treatment of children with neutropenia. In children weighing over 50 kg, the dose is the same as that for adults, including the aminoglyoside.
For children weighing less than 50 kg, the dose should be adjusted to 90 mg/kg CURITAZ (80 mg piperacillin/10 mg tazobactam) every six hours, in combination with an aminoglycoside.

Children aged 2 to 12 years of age hospitalized with intra-abdominal infection:

Weighing ≤ 40 kg: The recommended dose is 112,5 mg/kg CURITAZ every eight hours.

Weighing > 40 kg: The recommended dose is the same as that for adults i.e. 4,5 g CURITAZ every eight hours.

Renal insufficiency in children aged 2 to 12 years:

The pharmacokinetics of CURITAZ have not been studied in children with renal insufficiency. The following dosage adjustment is recommended according to the degree of actual renal impairment as follows:

Creatinine Clearance (ml/min)	**Recommended CURITAZ Dosage**
> 50	112,5 mg/kg eight hourly
< 50	78,75 mg/kg eight hourly

The above dosage modifications are only an approximation. Each patient must be monitored closely for signs of drug toxicity. Drug dose and interval should be adjusted accordingly.

Method of administration:

CURITAZ must be given by slow intravenous infusion (over 30 minutes).

4.3 Contraindications

Hypersensitivity to any of the β-lactams (including penicillins and cephalosporins) or to β-lactamase inhibitors (see section 4.4).

4.4 Special warnings and precautions for use

Use with caution in patients with:

- a history of sensitivity to multiple allergens – serious and occasionally fatal hypersensitivity (anaphylactic / anaphylactoid (including shock) reactions have been reported in patients receiving therapy with penicillins. There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe reactions when treated with a cephalosporin. If an allergic reaction occurs during therapy with CURITAZ, discontinue treatment immediately. Serious hypersensitivity reactions may require adrenaline (epinephrine) and other emergency measures. Before initiating therapy with CURITAZ

careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.

- Piperacillin / tazobactam may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalised exanthematous pustulosis (see section 4.8). If patients develop a skin rash they should be monitored closely and piperacillin/tazobactam discontinued if lesions progress.
- In patients with renal insufficiency or haemodialysis patients, the intravenous dose should be adjusted to the degree of renal function impairment (see section 4.2).
- a history of bleeding disorders, as penicillins, especially piperacillin, may cause platelet dysfunction and bleeding. This is more likely in patients with renal failure. If bleeding manifestations occur, the antibiotic should be discontinued and appropriate therapy instituted.
- cystic fibrosis, as they may be at increased risk of fever and skin rash.

CURITAZ has been associated with pseudomembranous colitis which can be fatal. It presents as severe abdominal pain with cramps, fever and severe watery stools which may become bloody. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment see section 4.8). Discontinue therapy with CURITAZ immediately and initiate suitable therapy (e.g. fluid and electrolyte management, protein supplementation and administration of an oral antibacterial agent effective against *Clostridium difficile*).

Preparations which inhibit peristalsis are contra-indicated.

Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of haematopoietic function should be performed.

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

As with other antibiotics, the possibility of the emergence of resistant organisms which might cause superinfections should be kept in mind, particularly during prolonged treatment.

As with other penicillins, patients may experience neuromuscular excitability or convulsions if

higher than recommended doses are given intravenously.

Pregnant and breastfeeding women should be treated only if the expected benefit outweighs the possible risks to the pregnant woman and foetus / infant (see section 4.6).

When CURITAZ is used concurrently with another antibiotic, especially an aminoglycoside, they should not be mixed in the same intravenous solution or administered concurrently due to physical incompatibility (see section 6,2).

This product contains 2,35 mmol (54 mg) of sodium per gram of piperacillin which may increase a patient's overall sodium intake. This may be harmful to people on a low sodium diet, such as those with renal impairment.

Serum potassium levels should be periodically determined in patients with low potassium reserves or who are receiving concomitant medications that may lower potassium levels, as hypokalaemia may occur.

Haemophagocytic lymphohistiocytosis (HLH)

Cases of HLH have been reported in patients treated with piperacillin/ tazobactam, often following treatment longer than 10 days. HLH is a life-threatening syndrome of pathologic immune activation characterised by clinical signs and symptoms of an excessive systemic inflammation (e.g., fever, hepatosplenomegaly, hypertriglyceridaemia, hypofibrinogenaemia, high serum ferritin, cytopenias and haemophagocytosis). Patients who develop early manifestations of pathologic immune activation should be evaluated immediately. If diagnosis of HLH is established, piperacillin / tazobactam treatment should be discontinued.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of CURITAZ with:

Anticoagulants, heparin, thrombolytic agents or other medicines affecting the blood coagulation system: may increase the risk of haemorrhage as CURITAZ inhibits platelet aggregation. Patients should be monitored carefully for signs of bleeding.

Methotrexate: may result in a reduction of methotrexate excretion. Serum levels should be monitored to avoid methotrexate toxicity.

Nondepolarizing muscle relaxants such as vecuronium: may prolong neuromuscular blockade.

Probenecid

Concurrent administraion of probenecid and CURITAZ produced a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either medicine are unaffected.

Vancomycin

Studies have detected an increased incidence of acute kidney injury in patients concomitantly administered piperacillin/tazobactam and vancomycin as compared to vancomycin alone (see section 4.4). Some of these studies
have reported that the interaction is vancomycin dose-dependent. No interactions have been found between CURITAZ and vancomycin or tobramycin.

Effects on laboratory tests

The administration of CURITAZ may result in a false-positive reaction for glucose in the urine using a copper-reduction method. It is recommended that glucose tests based on enzymatic glucose oxidase reaction be used.
There have been reports of positive test results using the Bio-Rad Laboratories Platelia *Aspergillus* EIA test in patients receiving CURITAZ 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 CURITAZ should be interpreted cautiously and confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Pregnancy:

Safety and efficacy in pregnancy and lactation has not been established.

Lactation:

Both piperacillin and tazobactam cross the placenta and piperacillin is excreted in low concentrations in breast milk.

4.7 Effects on ability to drive and use machines

CURITAZ is not known to affect ability to drive or operate machines.

4.8 Undesirable effects

Infections and infestations:

Less frequent: Candida infection*

Less frequent: Pseudomembranous colitis

Blood and lymphatic system disorders:

Frequent: Thrombocytopenia, anaemia*, leukopenia.

Less frequent: Agranulocytosis

Frequency unknown: pancytopenia*,neutropenia, haemolytic anaemia*,

thrombocytosis*,eosinophilia*

Immune system disorders:

Frequency unknown:

Hypersensitivity reaction*, anaphylactic/anaphylactoid reaction (including shock) *.

Metabolism and nutrition disorders:

Less frequent: Hypokalaemia

Psychiatric disorders:

Frequent: Insomnia

Frequency unknown: Delirium*

Nervous system disorders:

Frequent: Headache

Less frequent: Seizure*

Vascular disorders:

Less frequent: Hypotension, phlebitis, thrombophlebitis, flushing

Respiratory, thoracic and mediastinal disorders

Less frequent: Epistaxis

Frequency unknown: Eosinophilic pneumonia

Gastrointestinal disorders:

Frequent: Diarrhoea, abdominal pain, vomiting, constipation, nausea, dyspepia

Less frequent: Stomatitis

Hepatobiliary disorders:

Frequency unknown: Jaundice, hepatitis*

Skin and subcutaneous tissue disorders

Frequent: Rash, pruritus

Less frequent: erythema multiforme*,urticaria, rash maculopapular*, toxic epidermal necrolysis*

Frequency unknown: Stevens-Johnson syndrome *, dermatitis exfoliative, drug reaction with eosinophilia and systemic symptoms (DRESS)*, acute generalised exanthematous pustulosis (AGEP)*, dermatitis, bullous, purpura

Musculoskeletal and connective tissue disorders:

Less frequent: Arthralgia, myalgia

Renal and urinary disorders:

Frequency unknown: Renal failure, tubulointerstitial nephritis*

General disorders and administration site conditions:

Frequent: pyrexia, injection, site reaction, chills

Investigations:

Frequent: Alanine minotransferase increased, aspartate aminotransferase increased, protein total decreased, blood albumin decreased, Coombs direct test positive, blood creatinine increased, blood alkaline phosphatase increased, blood urea increased, activated partial thromboplastin time prolonged

Less frequent: blood glucose decreased, blood bilirubin increased, prothrombin time prolonged

Frequency unknown: Bleeding time prolonged, gammaglutamyltransferase Increased

*ADR identified post marketing

Piperacillin therapy has been associated with an increased incidence of fever and rash in cystic fibrosis patients.

Beta-lactam antibiotic class effects

Beta-lactam antibiotics, including piperacillin tazobactam, may lead to manifestations of encephalopathy and convulsions (see section 4.4).

4.9 Overdose

See section 4.4. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure). Treatment is symptomatic and supportive. No specific antidote is known. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis. In case of motor excitability or convulsions, anticonvulsive agents (e.g., diazepam or barbiturates) may be indicated. Emergency measures should be carried out in the case of severe, anaphylactic reactions, including oxygen, airway management, antihistamines, corticosteroids and sympathomimetics.

Consider the possibility of antibiotic-induced life-threatening pseudomembranous colitis in the case of severe persistent diarrhoea and discontinue CURITAZ immediately. Start treatment with appropriate therapy such as oral teicoplanin or oral vancomycin and avoid agents that inhibit peristalsis.

5. PHARMACOLOGICAL PROPERTIES

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, combinations of penicillins, including beta-lactamase
inhibitors
ATC code: J01CR05

Mechanism of action

Piperacillin is a broad-spectrum semi-synthetic penicillin with bactericidal activity. Penicillins bind to enzymes that are vital for the development of the bacterial cell wall during growth and division, inactivating them and thereby exerting a bactericidal activity through inhibition of both septum and cell wall synthesis.
Tazobactam is a penicillanic acid sulfone β-lactamase inhibitor.
The β-lactamase inhibitors bind irreversibly to β-lactamases, thereby protecting the penicillin from hydrolysis. Tazobactam combined with piperacillin enhances and extends the spectrum of the antibacterial activity of piperacillin against β-lactamase-producing bacteria.

Spectrum of in vitro activity:

Gram-positive bacteria: β-lactamase producing and non-producing strains of streptococci (*S. pneumoniae, S. pyogenes, S. agalactiae, S. viridans*, Group C, Group G), *Staphylococcus aureus, S. epidermidis* (coagulase-negative staphylococci) and *Enterococcus faecalis*.
Gram-negative bacteria: Most plasmid mediated β-lactamase producing and non-producing strains of *Escherichia coli*, *Haemophilus influenzae*, *H. parainfluenzae*, *Klebsiella* spp

(including *K. oxytoca, K. pneumoniae*), *Moraxella* spp. (including *Branhamella catarrhalis*), *Morganella morganii, Neisseria gonorrhoeae, Neisseria meningitides, Proteus vulgaris, Proteus mirabilis, Serratia* spp. (including *S. marcescens*) and *P. aeruginosa*.
Anaerobic bacteria: β-lactamase producing and non-producing anaerobes such as *Bacteroides* spp. (including *B. melaninogenicus*), the *Bacteroides fragilis* group including *B. fragilis, B. distasonis*, as well as, *Peptostreptococcus* spp., *Fusobacterium* spp., and *Clostridia* spp. (including *C. difficile, C. perfringens*).

The prevalence of acquired resistance may vary geographically and with time for selected species. Local information of resistance is desirable, particularly when treating severe infections. This information provides guidance on micro-organisms susceptible to piperacillin/tazobactam.
In vitro sensitivity does not necessarily imply *in vivo* efficacy.

5.2 Pharmacokinetic properties:

Peak piperacillin and tazobactam plasma concentrations are attained immediately after completion of an intravenous infusion or injection. Piperacillin and tazobactam are widely distributed in tissue and body fluids including intestinal mucosa, gallbladder, lung, bile and bone.
Both piperacillin and tazobactam are 20 to 30 % protein bound.
Piperacillin is hepatically metabolized to the desethyl metabolite, which has minor activity and tazobactam is hepatically metabolised to a single, inactive metabolite.
The plasma half-life of piperacillin and tazobactam range from 0,7 to 1,2 hours.
Approximately 68 % and 80 % of an administered dose of piperacillin and tazobactam, respectively, are excreted unchanged in the urine. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance. The increase is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance of below 20 mℓ/min compared to patients with normal renal function. Haemodialysis removes 30 to 50 % of the combination, with an additional 5 % of the tazobactam dose removed as the tazobactam metabolite. Peritoneal dialysis removes approximately 6 % and 21 % of the

piperacillin and tazobactam doses, respectively, with up to 18 % of the tazobactam dose removed as the tazobactam metabolite.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

CURITAZ should not be mixed with any other medicines in the same syringe, infusion bottle, intravenous bag, bottle, or tubing since compatibility has not been established.

Due to chemical instability, CURITAZ should not be used in solutions containing sodium bicarbonate.

CURITAZ should not be added to blood products or albumin hydrolysates.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Dry powder: Store at or below 25 °C.

Reconstituted solution: Store for 24 hours at 2 to 8 °C.

Any unused solution must be discarded.

KEEP OUT OF THE REACH OF CHILDREN.

6.5 Nature and contents of container

Curitaz™ 4,5 Powder for solution for infusion is available in 100 ml clear glass bottles with grey bromobutyl rubber stoppers and plastic flip-off caps.

Pack size:

1

6.6 Special precautions for disposal and other handling

Directions for reconstitution:

Each bottle CURITAZ should be reconstituted with at least 20 ml of one of the following diluents and shaken well until dissolved:

- sterile water for injection;
- sodium chloride 0,9 % solution in water for injection(1);
- glucose 5 % solution in water for injection;
- glucose 5 % solution in sodium chloride 0,9 % solution.

For intravenous infusion, the reconstituted solution can be further diluted to 50 ml with water for injection; and to the desired volume (eg. 50 ml, 100 ml or 150 ml) with either one of the following diluents:

- sodium chloride 0,9 % solution in water for injection;
- glucose 5 % solution in water for injection;
- dextran (grade 40) 6 % solution in sodium chloride 0,9 % solution;
- lactate Ringer's solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Sandoz SA (Pty) Ltd[1]

Waterfall 5-lr

Magwa Crescent West

Waterfall City

Jukskei View

2090

[1]Company Reg. No.: 1990/001979/07

8. REGISTRATION NUMBER

42/20.1.1/0004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

9 December 2008

10. DATE OF REVISION OF THE TEXT

13 May 2022