**Professional Information**

**SCHEDULING STATUS**

S4

**PROPRIETARY NAMES (and dosage forms)**

**RAZOBIN 2** (Lyophilised powder for solution for injection/infusion)

**RAZOBIN 3** (Lyophilised powder for solution for injection/infusion)

**RAZOBIN 4** (Lyophilised powder for solution for injection/infusion)

**COMPOSITION**

**RAZOBIN 2**

Each vial contains piperacillin sodium and tazobactam sodium cryodessicated powder for solution for injection/infusion equivalent to piperacillin 2,0 g and tazobactam 0,25 g. Each vial contains 4, 7 milli-equivalents (108 mg) of sodium.

**RAZOBIN 3**

Each vial contains piperacillin sodium and tazobactam sodium cryodessicated powder for solution for injection/infusion equivalent to piperacillin 3,0 g and tazobactam 0,375 g. Each vial contains 7, 05 milli-equivalents (162 mg) of sodium.

**RAZOBIN 4**

Each vial contains piperacillin sodium and tazobactam sodium cryodessicated powder for solution for injection/infusion equivalent to piperacillin 4,0 g and tazobactam 0,5 g. Each vial contains 9, 40 milli-equivalents (216 mg) of sodium.

**PHARMACOLOGICAL CLASSIFICATION**

A 20.1.1 Broad and medium spectrum antibiotics

## PHARMACOLOGICAL ACTION

**Pharmacodynamics:**

Piperacillin is a broad spectrum, semi-synthetic penicillin. It is active against many Gram-positive and Gram-negative aerobic and anaerobic bacteria, and exerts bactericidal activity by inhibition of both septum and cell wall synthesis. Tazobactam, a triazolylmethyl penicillanic acid sulfone, is an inhibitor of many β- lactamases, including the plasmid and chromosomally mediated enzymes. The antibiotic spectrum of piperacillin is enhanced and extended by the presence of tazobactam in the piperacillin/tazobactam formulation.

A wide range of gram-positive and gram-negative organisms are susceptible to **RAZOBIN**.

The following are resistant:

- Piperacillin-tazobactam-resistant *Pseudomonas aeruginosa*
- Incidence of cross-resistance with other antipseudomonal penicillins
- All methicillin-resistant staphylococci

**Pharmacokinetics:**

**Absorption**: Peak plasma concentrations of piperacillin and tazobactam are attained immediately after completion of an intravenous infusion of **RAZOBIN**.

**Metabolism**: Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite that lacks pharmacological and antibacterial activities.

**Excretion**: Both piperacillin and tazobactam are eliminated via the kidney by glomerular filtration and tubular secretion. Piperacillin is excreted rapidly as unchanged substance, with 68 % of the administered dose excreted in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion with 80 % of the administered dose excreted as unchanged substance and the remainder as the single metabolite. Piperacillin, tazobactam and desethyl piperacillin are also secreted into the bile.

**Plasma protein binding:** Both piperacillin and tazobactam are approximately 30 % bound to plasma proteins. The protein binding of either piperacillin or tazobactam is unaffected by the presence of the other compound. Protein binding of the tazobactam metabolite is negligible.

**Distribution**: Piperacillin and tazobactam are widely distributed into tissues and body fluids including intestinal mucosa, gallbladder, lung, female reproductive tissues (uterus, ovary, and fallopian tube), interstitial fluid, and bile. Mean tissue concentrations are generally 50 % to 100 % of those in plasma. Distribution of piperacillin and tazobactam into cerebrospinal fluid is low in subjects with non-inflamed meninges.

**Special Populations:**

**Patients with renal insufficiency**: After the administration of single doses of piperacillin/tazobactam to subjects with renal impairment, the half-life of piperacillin and of tazobactam increases with decreasing creatinine clearance. The increase in half-life in two-fold and four-fold for piperacillin and tazobactam, respectively at creatinine clearance below 20mL/min compared to patients with normal renal function. Dosage adjustments for piperacillin and tazobactam are recommended in patients where creatinine clearance is below 40 mL/min receiving the usual recommended daily dose piperacillin and tazobactam (See **"DOSAGE AND DIRECTIONS FOR USE"**).

**Patients with hepatic insufficiency:** The half-life of piperacillin and of tazobactam increases by approximately 25 % and 18 %, respectively, in patients with hepatic cirrhosis compared to healthy patients.

**INDICATIONS**

**RAZOBIN** 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:***

1. Community acquired pneumonia due to *Haemophilus influenzae.*
2. Intra-abdominal infections caused by piperacillin-resistant beta-lactamase-producing strains of *Escherichia coli* and *Bacteroides fragilis.*
3. Skin and skin structure infections caused by piperacillin-resistant beta-lactamase-producing strains of *Staphylococcus aureus.*
4. In neutropenic patients, **RAZOBIN** plus an aminoglycoside is indicated for bacterial infections.
5. Gynaecological infections including endometritis caused by piperacillin-resistant beta-lactamase-producing strains of *E.coli.*

**Children:**

*CHILDREN UNDER THE AGE OF 12 YEARS:*

In neutropenic patients, **RAZOBIN** plus an aminoglycoside is indicated for bacterial infections.

*CHILDREN 2-12 YEARS:*

**RAZOBIN** is indicated for the treatment of serious intra-abdominal infections, caused by *E.coli* or Bacteroides species, in hospitalised children aged 2 to 12 years. For paediatric patients below the age of 2 years, **RAZOBIN** has not been evaluated in this indication.

**CONTRA-INDICATIONS**

**RAZOBIN** is contra-indicated in patients with a history of allergic reactions to any of the penicillins and/or cephalosporins or β-lactamase inhibitors or any of the constituents of **RAZOBIN**.

Safety in pregnancy and lactation has not been established (see "**PREGNANCY AND LACTATION"**).

**WARNINGS AND SPECIAL PRECAUTIONS**

Serious and occasionally fatal hypersensitivity (anaphylactic/anaphylactoid including shocks) reactions have been reported in patients receiving therapy with penicillins. These reactions are more apt to occur in persons with a history of penicillin hypersensitivity or a sensitivity to multiple allergens. There have been reports of patients with a history of penicillin hypersensitivity who have experienced severe hypersensitivity reactions when treated with a cephalosporin. Careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens, before initiating therapy with **RAZOBIN**.

If an allergic reaction occurs during therapy with **RAZOBIN**, the antibiotic should be discontinued. Serious hypersensitivity reactions require immediate emergency measures, with epinephrine (adrenaline), corticosteroids and antihistamines. An open airway must be maintained.

Pseudomembranous colitis has been reported. Antibiotic-induced pseudomembranous colitis may occur manifesting in symptoms of severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis may occur during or after antibacterial treatment. Therefore, in patients who present with diarrhoea subsequent to the administration of antibacterial agents, it is important to consider this diagnosis. After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to **RAZOBIN** discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes; protein supplementation and treatment with an oral antibacterial medicine effective against *Clostridium difficile.*

Periodic assessment of organ system functions including renal and hepatic during prolonged therapy is advisable. Leukopenia and neutropenia may occur, especially during prolonged therapy. Therefore, periodic assessment of haematopoietic function should be performed. In some patients receiving β-lactam antibiotics, bleeding manifestations have occurred. These reactions have sometimes been associated with abnormalities of coagulation tests such as clotting time, platelet aggregation and prothrombin time and are more likely to occur in patients with renal failure. **RAZOBIN** should be discontinued and appropriate therapy instituted if bleeding manifestations occur.

The possibility of the emergence of resistant organisms, which may cause superinfections, should be kept in mind, particularly during prolonged treatment. If this occurs, appropriate measures should be taken. As with other penicillins, if higher than recommended doses are given intravenously, patients may experience convulsions or neuromuscular excitability. This product contains 2, 35 mEq (54 mg) of sodium per gram of piperacillin which may increase a patient's overall sodium intake. In patients with low potassium reserves,

periodic electrolyte determinations should be made and the possibility of hypokalaemia should be kept in mind with patients who have potentially low potassium reserves and who are receiving diuretics or cytotoxic therapy. Modest elevation of indices of liver function may be observed.

In patients with renal insufficiency or haemodialysis patients, the intravenous dose should be adjusted to the degree of renal function impairment. Patients over 65 years are not at an increased risk of developing adverse effects solely because of age. However, dosage should be adjusted in the presence of renal insufficiency.

**Haemophagocytic lymphohistiocytosis (haemophagocytic syndrome):**

Haemophagocytic lymphohistiocytosis may occur. Patients should be carefully monitored, and if any abnormalities such as pyrexia, rash, neurological symptoms, splenomegaly, swollen lymph nodes, cytopenia, increased LDH, hyperferritinaemia, hypertriglyceridaemia, hepatic impairment, or coagulation abnormalities are observed, administration of **RAZOBIN** should be discontinued, and appropriate measures should be taken.

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

There is no information to show that **RAZOBIN** affects the ability to drive a car or operate machinery.

**INTERACTIONS**

**Interactions with Other Medicines:**

No interaction is found between **RAZOBIN** and vancomycin.

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

The pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment was not significantly altered by piperacillin either alone or with tazobactam. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration.

Whenever **RAZOBIN** is used concurrently with another antibiotic, especially an aminoglycoside, the medicines must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility.

During simultaneous administration of high doses of heparin, oral anticoagulants and other medicines that may affect the blood coagulation system and/or the thrombocyte function, the coagulation parameters should be monitored regularly and tested more frequently. Piperacillin has been implicated in the prolongation of the neuromuscular blockage of vecuronium, when given concomitantly with vecuronium. Due to their similar mechanism of action, it is expected that the neuromuscular blockade produced by any of the non-depolarising muscle relaxants could be prolonged in the presence of piperacillin.

Since piperacillin may reduce the excretion of methotrexate; the serum levels of methotrexate should be monitored in patients to avoid medicine toxicity.

**Pharmaceutical Incompatibilities:**

**RAZOBIN** should not be mixed with other medicines in a infusion bottle or syringe since compatibility has not been established. Whenever **RAZOBIN** is used concurrently with another antibiotic (e.g. aminoglycosides), the medicines must be administered separately. The mixing of **RAZOBIN** with an aminoglycoside *in vitro* can result in the aminoglycoside being substantially inactivated.

**RAZOBIN** should not be used with solutions containing only sodium bicarbonate, because of chemical instability.

Lactated Ringer's solution is not compatible with **RAZOBIN**.

**RAZOBIN** should not be added to albumin hydrolysates or blood products.

**Laboratory Tests:**

There have been reports of positive test results using the Bio-Rad Laboratories Platella Aspergillus EIA test in patients receiving **RAZOBIN** injection who were subsequently found to be free of Aspergillus infection. Cross-reactions with non-Aspergillus polysaccharides and polyfuranoses with Bio-Rad Laboratories Platella Aspergillus EIA test have been reported. Therefore, positive test results in patients receiving **RAZOBIN** should be interpreted cautiously and confirmed by other diagnostic methods. The administration of **RAZOBIN** may result in a false-positive reaction for glucose in the urine using a copper-reduction method. Therefore, it is recommended that glucose tests based on enzymatic glucose oxidase reactions should be used.

**PREGNANCY AND LACTATION**

Safety in pregnancy and lactation has not been established.

Adequate studies on the use of **RAZOBIN** during pregnancy and the period of breast feeding are not available. **RAZOBIN** did not affect fertility in rats and was not teratogenic in rats or mice. Piperacillin and tazobactam cross the placenta. Piperacillin is excreted in low concentrations in human milk. Tazobactam concentrations in human milk have not been studied.

**DOSAGE AND DIRECTIONS FOR USE**

**RAZOBIN** may be given by slow intravenous infusion over a 30 minute period.

**Adults and Children 12 years and older:**

The usual dosage for adults and juveniles with normal renal function is 4/0,5 g piperacillin/tazobactam given every eight hours.

The dosage in immunocompromised and neutropenic patients with infection is 4/0, 5 g piperacillin/tazobactam every 6 hours in combination with an aminoglycoside.

**Children under the age of 12 Years:**

**RAZOBIN** is only recommended for the treatment of children with neutropenia.

For children weighing over 50 kg, follow the adult dosing guidance, including the aminoglycoside.

For children with normal renal function and weighing less than 50 kg, the dose should be adjusted to 90 mg/kg (80 mg piperacillin/10 mg tazobactam) administered every 6 hours, in combination with an aminoglycoside.

**Renal Insufficiency:**

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:

| INTRAVENOUS DOSAGE SCHEDULE FOR ADULTS WITH IMPAIRED RENAL FUNCTION | |
|---|---|
| Creatinine Clearance (ml/min) | Recommended Piperacillin/Tazobactam Dosage |
| 90 - 40 | 12 g/1,5 g/day in divided doses of 4 g/0,5 g every 8 hours or 3 g/0,375 g every 6 hours |
| 20 - 40 | 8 g/1,0 g/day in divided doses of 2 g/0,25 g every 6 hours |
| < 20 | 6 g/0,75 g/day in divided doses of 2 g/0,25 g every 8 hours |

For patients on haemodialysis, the maximum daily dose is 2 g/0,25 g every 8 hours piperacillin/tazobactam. In addition, because haemodialysis removes 30 % - 40 % of piperacillin in 4 hours, one additional dose of 0,75 g piperacillin/tazobactam should be administered following each dialysis period. For patients with renal

failure and hepatic insufficiency, measurement of serum levels of piperacillin/tazobactam will provide additional guidance for adjusting dosage.

**Neutropenic Patients:**

In treating neutropenic patients, full therapeutic doses of **RAZOBIN** and an aminoglycoside should be used. The possibility of hypokalaemia should be kept in mind in patients who have low potassium reserves, and periodic electrolyte determinations should be made in these patients.

**Duration of Therapy:**

In acute infections, treatment with **RAZOBIN** should be for a minimum of five days and continued for forty-eight hours beyond resolution of clinical symptoms or the fever.
The usual duration of treatment is 7 - 10 days.

**Hospitalised Children with intra-abdominal infection:**

For children aged 2 to 12 years, weighing up to 40 kg, and with normal renal function, the recommended dosage is 112,5 mg/kg (100 mg piperacillin / 12,5 mg tazobactam) every 8 hours.
For children aged 2 to 12 years, weighing over 40 kg, and with normal renal function, follow the adult dose guidance, i.e. 4,5 g (4 g piperacillin / 0,5 g tazobactam) every 8 hours.
The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. Therapy is recommended to be a minimum of 5 days and a maximum of 14 days, considering the dose administration should continue at least 48 hours after the resolution of clinical signs and symptoms.

**Children Aged 2 –12 Years with Renal Insufficiency:**

The pharmacokinetics of **RAZOBIN** have not been studied in paediatric patients with renal impairment. The following dosage adjustment for paediatric patients aged 2 to 12 years with renal impairment is recommended.

| INTRAVENOUS DOSAGE SCHEDULE FOR CHILDREN<br>AGED 2 – 12 YEARS WITH IMPAIRED RENAL FUNCTION | |
|---|---|
| Creatinine Clearance<br>(ml/min) | Recommended Piperacillin/Tazobactam<br>Dosage |
| > 50 | 112,5 mg/kg (100 mg / 12,5 mg) every 8 hours |
| ≤ 50 | 78,75 mg/kg (70 mg / 8,75 mg) every 8 hours |

The dosage modification is only an approximation. Each patient must be monitored closely for signs of medicine toxicity. Medicine dose and interval should be adjusted accordingly.

**Reconstitution Directions:**

***Diluents for Reconstitution:*** **(See "INTERACTIONS: Pharmaceutical Incompatibilities")**

Sterile Water for Injection.

Sodium Chloride Injection.

Each vial of 2 g/0, 25 g **RAZOBIN** should be reconstituted with at least 10 mL of one of the above diluents. Shake until dissolved.

Each vial of 3 g/0,375 g **RAZOBIN** should be reconstituted with at least 15 mL of one of the above diluents. Shake until dissolved.

Each vial of 4 g/0, 5 g **RAZOBIN** should be reconstituted with at least 20 mL of one of the above diluents.

Shake until dissolved.

***For intravenous infusion:***

The reconstituted solution may be further diluted to the desired volume (e.g. 50 mL - 150 mL) with one of the reconstitution diluents or with: Dextrose 5 % in water.

**SIDE-EFFECTS**

**Infections and infestations:**

*Less frequent:* Candidal superinfections

**Blood and the lymphatic system disorders:**

*Less frequent:* Leukopenia, neutropenia, thrombocytopenia, anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged),eosinophilia, haemolytic anaemia, agranulocytosis, Coombs direct test positive, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis

**Immune system disorders:**

*Less frequent:* Hypersensitivity reaction, anaphylactic/anaphylactoid reaction (including shock)

**Metabolism and nutrition disorders:**

*Less frequent:* Hypoalbuminaemia, hypoglycaemia, hypoproteinaemia, hypokalaemia

**Psychiatric disorders:**

*Less frequent:* Hallucinations, confusion, depression

**Nervous system disorders:**

*Less frequent:* Headache, insomnia, muscular weakness, convulsion, dry mouth

**Cardiac disorders:**

*Less frequent:* Tachycardia, including supraventricular and ventricular; bradycardia; dysrhythmia, including atrial fibrillation, ventricular fibrillation, cardiac arrest, cardiac failure, circulatory failure, myocardial infarction

**Vascular disorders:**

*Less frequent:* Hypotension, phlebitis, thrombophlebitis, flushing

**Gastrointestinal disorders:**

*Frequent:* Diarrhoea, nausea, vomiting

*Less frequent:* Constipation, dyspepsia, jaundice, stomatitis, abdominal pain, pseudomembranous colitis

**Hepato-biliary disorders:**

*Less frequent:* increased alanine aminotransferase, increased aspartate aminotransferase, increased bilirubin, increased blood alkaline phosphatise, increased gamma-glutamyltransferase, hepatitis

**Skin and subcutaneous tissue disorders:**

*Frequent:* Rash

*Less frequent:* Pruritus, urticaria, erythema, bullous dermatitis, erythema multiforme, increased sweating, eczema, exanthema, Stevens-Johnson Syndrome, toxic epidermal necrolysis

**Musculoskeletal, connective tissue and bone disorders:**

*Less frequent:* Arthralgia, myalgia

**Renal and urinary disorders:**

*Less frequent:* increased blood creatinine, dysuria, urinary retention, interstitial nephritis, renal failure increased blood urea

**General disorders and administrative site conditions:**

*Less frequent:* Fever, injection site reaction, rigors, tiredness, oedema.

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

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

See **"SIDE-EFFECTS"**. The majority of events experienced during overdosage including nausea, vomiting and diarrhoea have also been reported with the usual recommended dosages. If higher than recommended doses are given intravenously, particularly in the presence of renal failure, patients may experience neuromuscular excitability or convulsions.

Treatment should be supportive and symptomatic according to the patient's clinical presentation. There is no known specific antidote. Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis. In the event or an emergency, all required intensive medical measures are indicated as in the case of piperacillin. In case of motor excitability or convulsions, anticonvulsive agents (e.g. diazepam or barbiturates) may be indicated. In case of severe, hyperallergic (anaphylactic) reactions, the usual countermeasures are to be initiated (antihistamines, corticosteroids, sympathicomimetic medicines and, if required, oxygen and airway management). The possibility of antibiotic-induced life-threatening pseudomembranous colitis must be taken into consideration in case of severe, persistent diarrhoea. Therefore, **RAZOBIN** must be discontinued immediately in such cases and suitable therapy be initiated (e.g. oral teicoplanin or oral vancomycin). Preparations, which inhibit peristalsis, are contraindicated.

**IDENTIFICATION**

A white to off - white cryodessicated powder. When reconstituted, a light yellow coloured, clear solution free from visible particulate matter is formed.

**PRESENTATION**

**RAZOBIN 2**

30 mL clear, colourless, tubular glass vials fitted with 20 mm grey colour bromo butyl rubber stoppers and sealed with 20 mm aluminium seal with a violet coloured PP disc.

**Pack size:** Single vial packed in printed carton with a package insert. Each vial contains piperacillin sodium and tazobactam sodium cryodessicated powder for injection equivalent to piperacillin 2,0 g and tazobactam 0,25 g.

**RAZOBIN 3**

30 mL clear, colourless, tubular glass vials fitted with 20 mm grey colour bromo butyl rubber stoppers and sealed with 20 mm aluminium seal with a light blue coloured PP disc.

**Pack size:**

Single vial packed in printed carton with a package insert. Each vial contains piperacillin sodium and tazobactam sodium cryodessicated powder for injection equivalent to piperacillin 3,0 g and tazobactam 0,375 g.

**RAZOBIN 4**

48 mL clear, colourless, tubular glass vials fitted with 20 mm grey colour bromo butyl rubber stoppers and sealed with 20 mm aluminium seal with a red coloured PP disc.

**Pack size:**

Single vial packed in printed carton with a package insert. Each vial contains piperacillin sodium and tazobactam sodium cryodessicated powder for injection equivalent to piperacillin 4,0 g and tazobactam 0,5 g.

**STORAGE INSTRUCTIONS:**

Dry Powder: Vials containing sterile **RAZOBIN** dry powder may be stored at controlled room temperature (at or below 25 °C). Keep the vial in the outer carton until required for use.

Solutions: Vials containing reconstituted solutions for intravenous use should be used immediately. Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C and 48 hours at 2 – 8 °C. RAZOBIN contains no preservatives, therefore reconstitution/dilution should take place in controlled and validated aseptic conditions.

**RAZOBIN** is for **single use** only. Any unused portion of the reconstituted/diluted solution must be discarded.

**KEEP OUT OF REACH OF CHILDREN.**

**REGISTRATION NUMBER**

RAZOBIN 2: 44/20.1.1/0080

RAZOBIN 3: 44/20.1.1/0081

RAZOBIN 4: 44/20.1.1/0082

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

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