PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

PROPRIETARY NAMES (AND DOSAGE FORM)

TAZIJECT 0,5 g (powder for injection)

TAZIJECT 1,0 g (powder for injection)

TAZIJECT 2,0 g (powder for injection)

COMPOSITION

Vials containing ceftazidime pentahydrate equivalent to 0,5 g,1,0 g or 2,0 g of ceftazidime.

Inactive ingredient: sodium carbonate.

PHARMACOLOGICAL CLASSIFICATION

A 20.1.1 Broad and medium spectrum antibiotics.

PHARMACOLOGICAL ACTION

Ceftazidime is a bactericidal cephalosporin antibiotic.

Bacteriology*:*

Ceftazidime is bactericidal in action, exerting its effect on target cell wall proteins and causing inhibition of cell wall synthesis. A wide range of pathogenic strains and isolates associated with hospital acquired infections are susceptible to ceftazidime *in vitro*, including resistant strains and multi-resistant strains. It is stable to most clinically important beta-lactamases produced by both Gram-negative and Gram-positive organisms including multi-resistant strains. Ceftazidime has high intrinsic activity *in vitro* and acts with few changes in minimum

inhibitory concentration (MIC) at varied inoculum levels. Ceftazidime has been shown to have *in vitro* activity against the following organisms:

Gram-negative:

Pseudomonas aeruginosa, Pseudomonas spp. (other), *Klebsiella pneumoniae, Klebsiella* spp. (other), *Proteus mirabilis, Proteus vulgaris, Morganella morganii* (formally *Proteus morganii*), *Proteus rettgeri, Providencia* spp., *Escherichia coli, Enterobacter* spp., *Citrobacter* spp., *Serratia* spp., *Salmonella* spp., *Shigella* spp., *Yersinia enterocolitica, Pasteurella multocida, Acinetobacter* spp., *Neisseria gonorrhoeae, Neisseria meningitides, Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae* (including ampicillin-resistant strains).

Gram-positive:

Micrococcus spp., *Streptococcus pyogenes,* Streptococcus Group B, *Streptococcus pneumoniae, Streptococcus mitis, Streptococcus* spp., excluding *Enterococcus (Streptococcus) faecalis. Bacteriodes* spp., are mostly resistant. Ceftazidime is not active *in vitro* against methicillin-resistant Staphylococci, *Streptococcus faecalis* and many other Enterococci, *Listeria monocytogenes, Campylobacter* spp., *or Clostridium difficile.*

After 1 gram I.M. injection, ceftazidime serum levels exceed MIC90 for more than 12 hours for Streptococcus Group A and B (except *Strep. faecalis), E. coli, Klebsiella* spp., *Proteus mirabilis, Proteus* spp. (indole positive), *Serratia* spp., *Citobacter* spp., *Salmonella* spp., and *Haemophilus influenzae.*

Ceftazidime is not active against the following bacteria:

Methicillin-resistant staphylococci, *Enterococcus (Streptococcus) faecalis, Clostridium difficile, Listeria monocytogenes, Campylobacter* spp.

Pharmacokinetics:

In healthy subjects, the serum half-life of ceftazidime is 1,8 hours (1,5 to 2 hours) and only slightly altered by dosage or route of administration. The half-life is prolonged in patients with impaired renal function. Ceftazidime has a low serum protein binding (10 %).

INDICATIONS

TAZIJECT is indicated for the treatment of the following infections when caused by susceptible organisms:

- **Severe infections including: septicaemia, bacteraemia, peritonitis, and in immunocompromised patients,** caused by *Streptococcus pyogenes,* Streptococcus Group B*, Streptococcus pneumoniae, Streptococcus mitis, Streptococcus* spp*., Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Salmonella* spp*., Acinetobacter* spp*., Yersinia enterocolitica, or Pasteurella multocida.*
- **Respiratory tract infections such as pneumonia, bronchopneumonia, and bronchitis including lung infections in patients with cystic fibrosis,** caused by *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Haemophilus parainfluenzae, Escherichia coli, Streptococcus pyogenes, Proteus mirabilis, Serratia* spp, or *Enterobacter* spp*.*
- **Ear, nose and throat infections,** caused by *Streptococcus pneumoniae, Haemophilus influenzae, Klebsiella pneumoniae, Haemophilus parainfluenzae, Escherichia coli, Streptococcus pyogenes, Proteus mirabilis, Serratia* spp, or *Enterobacter* spp*.*
- **Urinary tract infections,** caused by *Neisseria gonorrhoeae, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, Proteus vulgaris, Morganella morganii, Enterobacter* spp*., or Citrobacter* spp*.*

- **Skin and soft tissue infections,** caused by *Streptococcus pyogenes, Streptococcus* spp*., Escherichia coli, Enterobacter* spp*., Klebsiella pneumoniae, Proteus mirabilis, or Morganella morganii.*
- **Gastrointestinal, biliary and abdominal infections,** caused by *Escherichia coli, Klebsiella pneumoniae, Streptococcus* spp*., Salmonella* spp*., Shigella* spp*., or Yersinia enterocolitica.*

CONTRA-INDICATIONS

Hypersensitivity to cephalosporin antibiotics.

WARNINGS AND SPECIAL PRECAUTIONS

Great care should be taken if TAZIJECT is to be given to patients who are penicillin-sensitive. Care is also necessary in patients with known histories of allergy.

TAZIJECT should be given with caution to patients with renal impairment; a dosage reduction is necessary. Renal and haematological status should be monitored especially during prolonged and high-dose therapy.

TAZIJECT may interfere with the Jaffé method of measuring creatinine concentrations and may produce falsely high values; this should be borne in mind when measuring renal function.

Positive results to the direct Coombs' test have been found during treatment with TAZIJECT and these can interfere with blood cross-matching.

The urine of patients being treated with TAZIJECT may give false-positive reactions for glucose using copper-reduction reactions.

INTERACTIONS

The concomitant use of a nephrotoxic medicine such as the aminoglycoside gentamicin may increase the risk of kidney damage with TAZIJECT. There is also some evidence for enhanced nephrotoxicity with a loop diuretic like furosemide.

The renal excretion of TAZIJECT is inhibited by probenecid.

There may be antagonism between TAZIJECT and bacteriostatic antibacterials.

PREGNANCY AND LACTATION

The safety in pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

TAZIJECT is given by deep intramuscular injection, slow intravenous injection over 3 to 5 minutes, or intravenous infusion over up to 30 minutes.

Adults:

The usual dose for adults ranges from 1 g to 6 g daily in divided doses every 8 or 12 hours. The higher doses are used in severe infections especially in immunocompromised patients. In adults with cystic fibrosis who have pseudomonal lung infection, high doses of 90 to 150 mg per kg body-weight daily in 3 divided doses are used; up to 9 g daily has been given to adults with normal function. Single doses of more than 1 g should be given intravenously.

Children:

Children are usually given 30 to 100 mg per kg daily in 2 or 3 divided doses, but in severely ill children up to 150 mg per kg daily to a maximum of 6 g daily may be given in 3 divided doses.

Neonates and infants up to 2 months old:

A dose of 25 to 60 mg per kg daily in 2 divided doses is effective.

Elderly:

In the elderly, the dose should generally not exceed 3 g daily.

Renal impairment:

In patients with renal impairment the dosage of TAZIJECT may need to be reduced. Following a loading dose of 1 g, maintenance doses are based on the creatinine clearance.

Maintenance doses are:

Creatinine Clearance (ml/min)	*Recommended dosage*
31 to 50	1 g every 12 hours
16 to 30	1 g every 24 hours
6 to 15	0,5 g every 24 hours
< 5	0,5 g every 48 hours

In severe infections these doses may need to be increased by 50%. In these patients ceftazidime through serum concentrations should not exceed 40 µg/ml. In patients undergoing peritoneal dialysis a loading dose of 1g may be given followed by 500 mg every 24 hours; ceftazidime sodium may also be added to the dialysis fluid, usually 125 mg to 250 mg of ceftazidime for 2 litres of dialysis fluid. In patients undergoing haemodialysis a loading dose of 1 g is given and should be repeated after each dialysis period.

Administration:

TAZIJECT may be given intravenously or by deep intramuscular injection into a large muscle mass such as the upper outer quadrant of the gluteus maximus or lateral part of the thigh.

Instructions for reconstitution:

It is preferable to use freshly constituted solutions of TAZIJECT.

See table below for addition volumes and solution concentrations:

Vial size	Amount of diluent to be added (ml)	Approximate available volume (ml)	Approximate concentration (mg/ml)
0,5 g intramuscular 0,5 g intravenous	1,5 5,0	1,9 5,4	265 90
1,0 g intramuscular 1,0 g intravenous	3,0 5,0	3,7 5,8	270 170
2,0 g intravenous bolus	6,0	7,5	270

As the product dissolves, carbon dioxide is released and a positive pressure develops. For ease of use, it is recommended that the following techniques of reconstitution are adopted:

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent. Remove the syringe needle.
2. Shake to dissolve; carbon dioxide is released and a clear solution obtained in about 1 to 2 minutes.
3. Inspect the solution visually for particulate matter and clarity. The solution should only be used if it is clear and free from particles.
4. Invert the vial. With the syringe plunger fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the headspace. The withdrawn solution may contain small bubbles of carbon dioxide which should be expelled from the syringe before injection.

For short intravenous infusion (e.g. up to 30 minutes), 1 g or 2 g TAZIJECT may be dissolved in 50 ml Water for Injections as follows:

1. Insert the syringe needle through the vial closure and inject the recommended volume of diluent for intravenous use as per the table above. Remove the syringe needle.

2. Shake to dissolve; carbon dioxide is released and a clear solution obtained in about 1 to 2 minutes.
3. Invert the vial. With the syringe plunger fully depressed, insert the needle through the vial closure and withdraw the total volume of solution into the syringe (the pressure in the vial may aid withdrawal). Ensure that the needle remains within the solution and does not enter the headspace. The withdrawn solution may contain small bubbles of carbon dioxide which should be expelled from the syringe.
4. Transfer the reconstituted solution to a 50 ml Water for Injection infusion container. Shake the container until a clear solution is obtained.
5. Inspect the solution visually for particulate matter and clarity. The solution should only be used if it is clear and free from particles.
6. Set up for infusion use in the normal way.

Note: To preserve product sterility, it is important that a gas relief needle is not inserted through the vial closure before the product has dissolved.

These solutions may be given directly into the vein or introduced into the tubing of a giving set if the patient is receiving parenteral fluids.

TAZIJECT is compatible with the most commonly used intravenous fluids.

TAZIJECT is incompatible with aminoglycosides and vancomycin. Therefore it would be prudent to flush giving sets and intravenous lines between administration of these two agents.

TAZIJECT is less stable in Sodium Bicarbonate Injection than in other intravenous fluids.

SIDE EFFECTS

Blood and lymphatic system disorders:

Less frequent: Neutropenia and thrombocytopenia have been reported. Bleeding complications related to hypothrombinaemia and/or platelet dysfunction have occurred. Haemolytic anaemia may also occur.

Gastrointestinal disorders:

Less frequent: Gastro-intestinal adverse effects such as nausea, vomiting, and diarrhoea have been reported. Prolonged use may result in overgrowth of non-susceptible organisms and pseudomembranous colitis may develop.

Hepato-biliary disorders:

Less frequent: Transient increases in liver enzyme values have been reported. Hepatitis and cholestatic jaundice have occurred.

Immune system disorders (including skin reactions):

Frequent: The most common adverse effects are hypersensitivity reactions, including skin reactions, urticaria, eosinophilia, fever, reactions resembling serum sickness, and anaphylaxis.

Nervous system disorders:

Less frequent: Convulsions and other signs of CNS toxicity have been associated with high doses, especially in patients with severe renal impairment.

Renal and urinary disorders:

Less frequent: Nephrotoxicity has been reported. Acute renal tubular necrosis has followed excessive dosage and has also been associated with its use in older patients or those with pre-existing renal impairment or those with the concomitant administration of nephrotoxic medicines such as aminoglycosides. Acute interstitial nephritis is also a possibility as a manifestation of hypersensitivity.

General disorders and administration site conditions:

Less frequent: There may be pain at the injection site following intra-muscular administration, and thrombophlebitis has occurred following intravenous infusion. There may be a positive response to the Coombs' test.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See “Side effects”.

Serum levels of TAZIJECT are reduced by dialysis.

Treatment is supportive and symptomatic.

IDENTIFICATION

TAZIJECT is a white to off-white powder.

Reconstituted product: Clear yellow solution.

PRESENTATION

Packs for I.M., I.V. or for I.V. infusion containing:

Single dose clear glass vial with dry substance equivalent to 0,5 g ceftazidime in packs with 1 or 10 vials.

Single dose clear glass vial with dry substance equivalent to 1 g ceftazidime in packs with 1 or 10 vials.

Single dose clear glass vial with dry substance equivalent to 2 g ceftazidime in packs with 1 or 10 vials.

STORAGE INSTRUCTIONS

Store at or below 25 ºC in a dry place, protected from light. Keep vials in carton until required for use.

Reconstituted product: Store for 24 hours at or below 25 ºC or up to 48 hours in a refrigerator (2 to 8 ºC). Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

TAZIJECT 0,5 g : A 39/20.1.1/ 0125

TAZIJECT 1,0 g : A 39/20.1.1/ 0126

TAZIJECT 2,0 g : A 39/20.1.1/ 0127

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

Acino Pharma (Pty) Ltd

106 16th Road

Midrand

South Africa

DATE OF PUBLICATION OF THE PACKAGE INSERT

3 June 2005

Namibia only:

Scheduling Status: NS2

Taziject 0,5 g: Reg No 06/20.1.1/0249

Taziject 1,0 g: Reg No 06/20.1.1/0248

Taziject 2,0 g: Reg No 06/20.1.1/0247