APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TAPRANEM.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 4 g piperacillin (as sodium salt) and 0,5 g tazobactam (as sodium salt). Powder for solution for infusion.

Excipient(s) with known effect:

Each vial of TAPRANEM contains 207 mg sodium.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion.

A white or almost white powder or loose mass.

pH: 5,0 – 7,0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAPRANEM 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. Gynaecologic infections including endometritis caused by piperacillin resistant beta-lactamase producing strains of *E coli*.
5. TAPRANEM plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children

Children under the age of 12 years:

TAPRANEM plus an aminoglycoside is indicated for bacterial infections in neutropenic patients.

Children 2 - 12 years:

In hospitalised children aged 2 to 12 years, TAPRANEM is indicated for the treatment of serious intra-abdominal infections, caused by *E. coli* or *Bacteroides* species.

It has not been evaluated in this indication for paediatric patients below the age of 2 years.

While TAPRANEM is indicated only for the conditions listed above, infections caused by piperacillin susceptible organisms are also amenable to piperacillin/tazobactam treatment due to its piperacillin content. Therefore, the treatment of mixed infections caused by piperacillin susceptible organisms and ß-lactamase producing organisms susceptible to piperacillin/tazobactam should not require the addition of another antibiotic.

TAPRANEM is useful in the treatment of mixed infections and in presumptive therapy prior to the availability of the results of sensitivity tests.

4.2 Posology and method of administration

Posology

Adults and juveniles 12 years and older

The usual dosage for adults and juveniles with normal renal function is TAPRANEM 4 g/0,5 g given every eight hours. The dosage in immunocompromised and neutropenic patients with infection is TAPRANEM 4 g/0,5 g every 6 hours in combination with an aminoglycoside.

Duration of therapy

In acute infections, treatment with TAPRANEM 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.

For information on co-administration of TAPRANEM with aminoglycosides, refer to section 6.6.

Special populations

Elderly

TAPRANEM may be used at the same dose levels as adults except in cases of renal impairment (see below).

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:

Creatine clearance (ml/min)	**Recommended TAPRANEM dosage**
90 – 40	12 g/1,5 g / day in divided doses of 4 g/0,5 g q8h or 3 g/0,375 g q6h
20 – 40	8 g/1,0 g / day in divided doses of 2 g/0,25 g q6h
< 20	6 g/0,75 g / day in divided doses of 2 g/0,25 g q8h

For patients on haemodialysis, the maximum daily dose is 2 g/0,25 g every 8 hours TAPRANEM. In addition, because

haemodialysis removes 30 % - 40 % of piperacillin in 4 hours, one additional dose of 0,75 g TAPRANEM should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of TAPRANEM will provide additional guidance for adjusting dosage.

Neutropenic patients

In treating neutropenic patients, full therapeutic doses of TAPRANEM 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.

Paediatric population

Children under the age of 12 years

TAPRANEM 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.

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 piperacillin/tazobactam 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 aged 2-12 years with impaired renal function:

Creatine clearance (ml/min)	**Recommended TAPRANEM dosage**
> 50	112,5 mg/kg (100 mg/12,5 mg) q8h
< 50	78,75 mg/kg (70 mg/8,75 mg) q8h

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.

Method of administration

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

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to piperacillin/tazobactam, any penicillins and/or cephalosporins or ß-lactamase inhibitors, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Before initiating therapy with TAPRANEM, careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, other beta-lactam medicines (e.g. cephalosporin, monobactam or carbapenem) and other allergens. Serious and occasionally fatal hypersensitivity anaphylactic/ anaphylactoid (including shock) reactions have been reported in patients receiving therapy with penicillins, including piperacillin/tazobactam. These reactions are more likely to occur in persons with a history of sensitivity to multiple allergens. Serious hypersensitivity reactions require the discontinuation of TAPRANEM and may require administration of epinephrine (adrenaline), corticosteroids and antihistamines. An open airway must be maintained.

TAPRANEM may cause severe cutaneous adverse reactions, such as Stevens-Johnson syndrome, toxic epidermal

necrolysis, medicine 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 TAPRANEM discontinued if lesions progress.

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including piperacillin/tazobactam. Antibiotic-induced pseudomembranous colitis may be manifested by severe, persistent diarrhoea which may be life-threatening. The onset of pseudomembranous colitis symptoms may occur during or after antibacterial treatment. In these cases, TAPRANEM should be discontinued.

Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of TAPRANEM.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to medicine 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 *C. difficile.*

While TAPRANEM possesses the characteristic low toxicity of the penicillin group of antibiotics, 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.

Bleeding manifestations have occurred in some patients receiving beta-lactam antibiotics. These reactions sometimes have 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. If bleeding manifestations occur, TAPRANEM should be discontinued, and appropriate therapy instituted.

The selection of TAPRANEM to treat an individual patient should take into account the appropriateness of using a broad-spectrum semi-synthetic penicillin based on factors such as the severity of the infection and the prevalence of resistance to other suitable antibacterial medicines.

Therapy with TAPRANEM may result in the emergence of resistant organisms, which might cause super-infections, particularly during prolonged treatment.

Neurological complications in the form of convulsions (seizures) may occur when high doses are administered, especially in patients with impaired renal function (see section 4.8).

Renal impairment

Due to its potential nephrotoxicity (see section 4.8), TAPRANEM should be used with care in patients with renal impairment or in haemodialysis patients. Intravenous dosages and administration intervals should be adjusted to the degree of renal function impairment (see section 4.2).

Combined use of TAPRANEM and vancomycin may be associated with an increased incidence of acute kidney injury (see section 4.5).

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.

This medicine contains 207 mg sodium per vial, equivalent to 13 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

This should be taken into consideration for patients who are on a controlled sodium diet.

Hypokalaemia may occur in patients with low potassium reserves or those receiving concomitant medicines, who are receiving cytotoxic therapy or diuretics that may lower potassium levels; periodic electrolyte determinations may be advisable in such patients. patients. Modest elevation of indices of liver function may be observed.

4.5 Interaction with other medicines and other forms of interaction

Probenecid

Concurrent administration of probenecid and piperacillin/tazobactam, as in TAPRANEM produces a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either substances are unaffected.

Vancomycin

No pharmacokinetic interactions have been noted between piperacillin/tazobactam and vancomycin.

Aminoglycosides

Whenever TAPRANEM 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. Piperacillin (as contained in TAPRANEM), either alone or with tazobactam, did not significantly alter the pharmacokinetics of tobramycin in subjects with normal renal function and with mild or moderate renal impairment. The pharmacokinetics of piperacillin, tazobactam, and the M1 metabolite were also not significantly altered by tobramycin administration. The inactivation of tobramycin and gentamicin by piperacillin has been demonstrated in patients with severe renal impairment.

For information related to the administration of TAPRANEM with aminoglycosides please refer to sections 6.2 and 6.6.

Anticoagulants

During simultaneous administration of heparin, oral anticoagulants and other substances that may affect the blood coagulation system including thrombocyte function, appropriate coagulation tests should be performed more frequently and monitored regularly.

Non-depolarising muscle relaxants

Piperacillin, as contained in TAPRANEM, when used concomitantly with vecuronium has been implicated in the

prolongation of the neuromuscular blockade of vecuronium. Due to their similar mechanisms 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.

Methotrexate

Piperacillin, as contained in TAPRANEM, may reduce the excretion of methotrexate; therefore, serum levels of methotrexate should be monitored in patients to avoid substance toxicity.

Effects on laboratory tests

Non-enzymatic methods of measuring urinary glucose may lead to false-positive results. Therefore, enzymatic urinary glucose measurement is required under TAPRANEM therapy.

A number of chemical urine protein measurement methods may lead to false-positive results. Protein measurement with dip sticks is not affected.

The direct Coombs test may be positive.

Bio-Rad Laboratories *Platelia Aspergillus* EIA tests may lead to false-positive results for patients receiving TAPRANEM. Cross-reactions with non-*Aspergillus* polysaccharides and polyfuranoses with Bio-Rad Laboratories *Platelia Aspergillus* EIA test have been reported.

Positive test results for the assays listed above in patients receiving TAPRANEM should be confirmed by other diagnostic methods.

4.6 Fertility, pregnancy and lactation

Pregnancy

Safety and efficacy during pregnancy has not been established.

Breastfeeding

Safety and efficacy during breastfeeding has not been established. Piperacillin and tazobactam cross the placenta.

Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Women receiving TAPRANEM should not breastfeed their infants.

Fertility

Piperacillin/tazobactam did not affect fertility in rats and was not teratogenic in mice or rats.

4.7 Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent reported adverse reaction is diarrhoea.

Among the most serious adverse reactions pseudo-membranous colitis and toxic epidermal necrolysis occur less frequently. The frequencies for pancytopenia, anaphylactic shock and Stevens-Johnson syndrome cannot be estimated from the currently available data.

b. Tabulated list of adverse reactions

System organ class	Frequent	Less frequent	Frequency unknown
Infections and Infestations	Candida infection		

Blood and lymphatic system disorders	Thrombocytopenia	Leukopenia, agranulocytosis, anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia, Coombs direct test positive, pancytopenia, prolonged partial thromboplastin time, prothrombin time prolonged, thrombocytosis	Neutropenia
Immune system disorders			Anaphylactoid shock, anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity
Metabolism and nutrition disorders		Blood albumin decreased, blood glucose decreased, blood total protein decreased, hypokalaemia	
Nervous system disorders	Headache	Seizure, insomnia	
Vascular disorders		Hypotension, phlebitis, thrombophlebitis, flushing	
Respiratory, thoracic and mediastinal disorders		Epistaxis	Eosinophilic pneumonia
Gastrointestinal disorders	Diarrhoea, abdominal pain, vomiting, constipation,	Stomatitis, pseudomembranous colitis	

	nausea, dyspepsia		
Hepato-biliary disorders		Alanine aminotransferase increased, aspartate aminotransferase increased, Bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyl-transferase increased, hepatitis	Jaundice
Skin and subcutaneous tissue disorders	Rash	Pruritus, erythema multiforme, urticaria, bullous dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis	Dermatitis exfoliative, purpura, drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		Arthralgia, myalgia	
Renal and urinary disorders		Blood creatinine increased, interstitial	Tubulointerstitial nephritis

		nephritis, renal failure, blood urea nitrogen increased	
General disorders and administration site conditions	Pyrexia, injection site reaction	Fever, injection site reaction, rigors, chills	
Investigations	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	Blood glucose decreased, blood bilirubin increased, prothrombin time prolonged	Bleeding time prolonged, gamma-glutamyl-transferase increased

Post-marketing

System organ class	**Side effect**
Infections and infestations	Candidiasis
Blood and lymphatic system disorders	Pancytopenia, haemolytic anaemia, thrombocytosis, eosinophilia
Immune system disorders	Anaphylactoid shock, anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, hypersensitivity
Psychiatric disorders	Delirium
Hepatobiliary disorders	Hepatitis
Skin and subcutaneous tissue disorders	Erythema multiforme, maculopapular rash, toxic epidermal necrolysis, Stevens-Johnson syndrome, medicine reaction with eosinophilia and systemic symptoms (DRESS), acute generalised exanthematous pustulosis (AGEP)

Renal and urinary disorders	Tubulointerstitial nephritis

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 TAPRANEM, may lead to manifestations of encephalopathy and convulsions (see section 4.4).

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

4.9 Overdose

Symptoms

There have been post-marketing reports of overdose with piperacillin/tazobactam. The majority of those events experienced, including nausea, vomiting, and diarrhoea, have also been reported with the usual recommended dose. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

Treatment

In the event of an overdose, TAPRANEM treatment should be discontinued. No specific antidote is known.

Treatment should be supportive and symptomatic according to the patient's clinical presentation.

Excessive serum concentrations of either piperacillin or tazobactam may be reduced by haemodialysis (see section 4.4).

In the event of an emergency, all required intensive medical measures are indicated as in the case of piperacillin.

In case of motor excitability or convulsions, anticonvulsive medicines (e.g. diazepam or barbiturates) may be indicated.

In case of severe, hyperallergic (anaphylactic) reactions, the usual countermeasures are to be initiated (antihistamines, corticosteroids, sympathomimetic medicines and, if required, oxygen and airway management).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Antibacterials for systemic use, Combinations of penicillins incl. beta-lactamase inhibitors; ATC code: J01C R05.

Mechanism of action

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

The organisms that are inherently resistant to piperacillin-tazobactam are those organisms in which beta-lactam resistance is due to a change in a penicillin-binding protein (PBP). These include all methicillin-resistant staphylococci, penicillin-resistant streptococci and enterococci, and some penicillin-resistant *Haemophilus* and *Neisseria* where resistance is not due to a beta-lactamase. It needs to be noted, though, that not all beta-lactamases in *Enterobacteriaceae*, including *Escherichia coli*, are inhibited by tazobactam.

In vitro sensitivity does not necessarily imply clinical efficacy.

5.2 Pharmacokinetic properties

Absorption

The peak piperacillin and tazobactam concentrations after 4 g/0,5 g administered over 30 minutes by intravenous infusion are 298 µg/ml and 34 µg/ml respectively.

Distribution

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.

Piperacillin / tazobactam is widely distributed in tissues and body fluids including intestinal mucosa, gallbladder, lung, bile, and bone. 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, as with other penicillins.

Biotransformation

Piperacillin is metabolised to a minor microbiologically active desethyl metabolite. Tazobactam is metabolised to a single metabolite that has been found to be microbiologically inactive.

Elimination

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 appearing in the urine. Tazobactam and its metabolite are eliminated primarily by renal excretion, with 80 % of the administered dose appearing as unchanged substance and the remainder as the single metabolite. Piperacillin, tazobactam, and desethyl piperacillin are also secreted into the bile. Following single or multiple doses of piperacillin/tazobactam to healthy subjects, the plasma half-life of piperacillin and tazobactam ranged from 0,7 to 1,2 hours and was unaffected by dose

or duration of infusion. The elimination half-lives of both piperacillin and tazobactam are increased with decreasing renal clearance. There are no significant changes in piperacillin pharmacokinetics due to tazobactam. However, piperacillin reduces the rate of elimination of tazobactam.

Special populations

The half-life of piperacillin and of tazobactam increases by approximately 25 % and 18 %, respectively, in patients with hepatic cirrhosis compared to healthy subjects. Dosage adjustment of piperacillin is not warranted in patients with hepatic cirrhosis.

The half-life of piperacillin and tazobactam increases with decreasing creatinine clearance. The increase in half-life is two-fold and four-fold for piperacillin and tazobactam, respectively, at creatinine clearance below 20 ml/min compared to patients with normal renal function.

Haemodialysis removes 30 % to 50 % of piperacillin / tazobactam, 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.

Elderly patients

The mean half-life for piperacillin and tazobactam were 32 % and 55 % longer, respectively, in the elderly compared with younger subjects. This difference may be due to age-related changes in creatinine clearance.

Paediatric population

The clearance in paediatric population is comparable to adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

TAPRANEM must not be mixed with other medicines except those mentioned in section 6.6.

Whenever TAPRANEM is used concurrently with another antibiotic (e.g. aminoglycosides), the substances must be administered separately. The mixing of beta-lactam antibiotics with an aminoglycoside *in vitro* can result in substantial inactivation of the aminoglycoside (see section 4.5 and 6.6).

TAPRANEM should not be mixed with other substances in a syringe or infusion bottle since compatibility has not been established.

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

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

6.3 Shelf life

Unopened vial: 3 years.

Reconstituted solution

Vials containing reconstituted are stable for 24 hours at room temperature (below 25 °C) and 48 hours under refrigeration (2 - 8 °C).

Diluted reconstituted solution for infusion

Diluted solutions prepared for intravenous use are stable for 24 hours at room temperature (below 25 °C) and 48 hours under refrigeration (2 - 8 °C) in IV bags or syringes.

6.4 Special precautions for storage

Dry powder: Do not store above 30 °C and protect from moisture.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

Single use only. Discard any unused solution.

6.5 Nature and contents of container

50 ml Type II glass vial with grey bromobutyl rubber stopper and blue aluminium flip-off caps. The vials are packed into a cardboard carton -

1, 5, 10, 12, 25 or 50 vials per carton.

6.6 Special precautions for disposal and other handling

The reconstitution and dilution is to be made under aseptic conditions. The reconstituted solution is a clear, colourless solution essentially free from particle matter. The solution is to be inspected visually for particulate matter and discolouration prior to administration. The solution should only be used if the solution is clear and free from particles.

Reconstitution directions

Diluents for Reconstitution:

- Sterile Water for Injection
- Bacteriostatic Water for Injection
- 0,9 % (9 mg/ml) Sodium Chloride solution for injection

Each vial of TAPRANEM should be reconstituted with at least 20 ml of one of the above diluents. Shake until dissolved.

The reconstituted solution may be further diluted to the desired volume (e.g., 50 ml or 100 ml) with one of the reconstitution diluents or with Dextrose 5 % in water.

Co-Administration of TAPRANEM with aminoglycosides

Due to *in-vitro* inactivation of the aminoglycoside by the beta-lactam antibiotics, piperacillin/tazobactam and the aminoglycoside are recommended for separate administration. Piperacillin/tazobactam and the aminoglycoside should be reconstituted and diluted separately when concomitant therapy with aminoglycosides is indicated (see section 4.5).

In circumstances where co-administration is preferred, the reformulated piperacillin/tazobactam containing EDTA

supplied in vials is compatible for simultaneous co-administration via Y-site infusion only with the following aminoglycosides under the following conditions:

Aminoglycoside	**Piperacillin/ tazobactam (grams) dose**	**Piperacillin/ tazobactam diluent volume (ml)**	**Aminoglycoside concentration range * (mg/ml)**	**Acceptable diluents**
Amikacin	2.25, 3.375, 4.5	50, 100, 150	1.75 – 7.5	0,9 % sodium chloride or 5 % dextrose
Gentamicin	2.25, 3.375, 4.5	100, 150	0.7 – 3.32	0,9 % sodium chloride

* The dose of aminoglycoside should be based on patient weight, status of infection (serious or life-threatening) and renal function (creatinine clearance).

Compatibility of piperacillin/tazobactam with other aminoglycosides has not been established. Only the concentration and diluents for amikacin and gentamicin with the dosages of piperacillin/tazobactam listed in the above table have been established as compatible for co-administration via the Y-site. Simultaneous co-administration via Y-site in any other manner than listed above may result in inactivation of the aminoglycoside by piperacillin/tazobactam.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Ando Pharma (Pty) Ltd

73 Keurboom Crescent

Plattekloof

Cape Town

7500

8. REGISTRATION NUMBER(S)

56/20.1.1/0247

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

To be allocated by SAHPRA upon approval.

10. DATE OF REVISION OF THE TEXT