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| **Applicant:** Oethmaan Biosims (Pty) Ltd | **SAHPRA approval date:**<br>06 March 2025 |
| **Product:**<br>TAZLIN 4,5 | **Dosage form and strength:**<br>Each vial contains piperacillin sodium equivalent to 4 g piperacillin & tazobactum sodium equivalent to 500 mg tazobactum powder for solution for injection |

# PROFESSIONAL INFORMATION – APPROVED

## SCHEDULING STATUS:

S4

## 1. NAME OF THE MEDICINE:

**TAZLIN 4,5, Powder for solution for injection**

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each Tazlin 4,5 vial contains:

Piperacillin sodium equivalent to 4 g piperacillin

Tazobactum sodium equivalent to 500 mg tazobactum.

Contains 9,39 mmol (or 216 mg) sodium per vial.

Sugar free

For full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for solution for injection.

Tazlin 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.

Initial: 06-03-2025

## 4. CLINICAL PARTICULARS:

### 4.1 Therapeutic indications

TAZLIN 4,5 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, (TAZLIN 4,5 has not been evaluated for this indication in younger children).

Because of its broad spectrum of activity TAZLIN 4,5 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

### Posology

TAZLIN 4,5 must be given by slow intravenous infusion (over 30 minutes).

The duration of therapy should be guided by the severity of the infection and the patient's clinical and bacteriological progress. Treatment with TAZLIN 4,5 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 TAZLIN 4,5 plus 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 TAZLIN 4,5 (4 g piperacillin/500 mg tazobactam) given every 8 hours.

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

### Special populations

***Elderly with normal renal function:***

TAZLIN 4,5 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 TAZLIN 4,5 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 TAZLIN 4,5 every eight hours. In addition, because haemodialysis removes 30 to 50 % of piperacillin in 4 hours, one additional dose of 0,75 g TAZLIN 4,5 should be administered following each dialysis period. For patients with renal failure and hepatic insufficiency, measurement of serum levels of TAZLIN 4,5 will provide additional guidance for adjusting dosage.

***Children aged 12 years and under with normal renal function:***

TAZLIN 4,5 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 TAZLIN 4,5 (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 TAZLIN 4,5 every eight hours.

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

***Renal insufficiency in children aged 2 to 12 years:***

The pharmacokinetics of TAZLIN 4,5 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 TAZLIN 4,5 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 medicine toxicity. Medicine dose and interval should be adjusted accordingly.

**Method of administration**

TAZLIN 4,5 must be given by slow intravenous infusion (30 minutes).

Prior to administration, each vial of TAZLIN 4,5 must be reconstituted and may be further diluted to the desired volume. For information on instructions for reconstitution and dilution, see section 6.6.

**4.3 Contraindications**

- Hypersensitivity to any of the β-lactams (including penicillins and cephalosporins) or to β-lactamase inhibitors (see “section 4.4”) or to any excipients of TAZLIN 4,5 listed in section 6.1.

**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 TAZLIN 4,5, discontinue treatment immediately. Serious hypersensitivity reactions may require adrenaline (epinephrine) and other emergency measures. Before initiating therapy with TAZLIN 4,5 careful inquiry should be made concerning previous hypersensitivity reactions to penicillins, cephalosporins, and other allergens.
- renal insufficiency or on haemodialysis. The dosage of TAZLIN 4,5 must be adjusted (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.

**Serious skin reactions**

Serious skin reactions, such as erythema multiforme, bullous dermatitis, exanthema, toxic epidermal necrolysis, Stevens-Johnson syndrome have been reported (see section 4.8).
Patients should be monitored closely if they develop a skin rash and TAZLIN 4,5 should be discontinued if lesions progress.

***Clostridium difficile* associated diarrhoea, including colitis**

TAZLIN 4,5 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 TAZLIN 4,5 immediately and initiate suitable therapy (e.g. fluid and electrolyte management, protein supplementation and administration of an oral antibacterial medicine effective against *Clostridium difficile*). Preparations which inhibit peristalsis are contraindicated.

**Haematology**

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

**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 TAZLIN 4,5 should be discontinued, and appropriate measures should be taken.

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

**Resistance**

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.

**Neurological effects**

As with other penicillins, patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously.

When TAZLIN 4,5 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).

**Hypokalaemia**

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.

**Kounis Syndrome**:

Cases of Kounis syndrome, also known as allergic angina or allergic myocardial infarction, have been reported in association with the use of **TAZLIN 4,5**. Kounis syndrome is characterized by the concurrence of acute coronary syndromes with allergic or hypersensitivity reactions, leading to coronary artery spasm, plaque rupture, or stent thrombosis.

Patients with a history of allergies, hypersensitivity reactions, or cardiovascular disease may be at increased risk. Therefore, careful consideration should be given before prescribing **TAZLIN 4,5** to these patients. Close monitoring for signs and symptoms of an allergic reaction or myocardial ischemia is recommended.

In the event of an allergic reaction or signs suggestive of Kounis syndrome (e.g., chest pain, shortness of breath, palpitations), the administration of **TAZLIN 4,5** should be discontinued immediately and appropriate medical treatment initiated. Emergency measures should include the administration of epinephrine, antihistamines, corticosteroids, and other supportive treatments as indicated.

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***Linear IgA Bullous Dermatosis***:

Cases of Linear IgA bullous dermatosis (LABD) have been reported in association with the use of **TAZLIN 4,5**. LABD is an autoimmune blistering disorder characterized by the linear deposition of IgA at the basement membrane zone, presenting with blistering skin eruptions.

Healthcare professionals should be aware of this potential risk and monitor patients for signs and symptoms of LABD, such as:

- Itchy or painful blistering lesions, often arranged in a linear pattern
- Erosions and areas of denuded skin.

If signs or symptoms of LABD occur, **TAZLIN 4,5** should be discontinued immediately, and appropriate dermatological evaluation and treatment should be initiated.

**Sodium content**

This product contains 216 mg of sodium per vial, equivalent to 10,8 % of the WHO maximum daily intake of 2 g sodium for an adult.

**4.5 Interaction with other medicines and other forms of interaction**

Concomitant use of TAZLIN 4,5 with:

**Anticoagulants, heparin, thrombolytic medicines or other medicines affecting the blood coagulation system**: may increase the risk of haemorrhage as TAZLIN 4,5 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 administration of probenecid and TAZLIN 4,5 produced a longer half-life and lower renal clearance for both piperacillin and tazobactam; however, peak plasma concentrations of either medicine are unaffected.

**Other antibiotics**

TAZLIN 4,5 may also interact with bacteriostatic antibacterial medicines such as chloramphenicol and tetracyclines.

No interactions have been found between TAZLIN 4,5 and vancomycin or tobramycin.

Piperacillin either alone or with tazobactam did not significantly alter the pharmacokinetics of tobramycin in patients 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.

Whenever TAZLIN 4,5 is used concurrently with another antibiotic, especially an aminoglycoside such as tobramycin, the medicines must not be mixed in intravenous solutions or administered concurrently due to physical incompatibility (see sections 6.2 and 6.6).

**Oral contraceptives**

Effectiveness of oral contraceptives may be decreased by piperacillin/tazobactam, including TAZLIN 4,5.

**Laboratory tests**

The administration of TAZLIN 4,5 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 TAZLIN 4,5 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 TAZLIN 4,5 should be interpreted cautiously and confirmed by other diagnostic methods.

**4.6 Fertility, pregnancy and lactation**

Safety and efficacy in pregnancy and lactation has not been established. Adequate studies on the use of TAZLIN 4,5 during pregnancy and the period of breastfeeding are not yet available.

**Pregnancy**

Piperacillin and tazobactam cross the placenta.

Studies in animals have shown developmental toxicity, but no evidence of teratogenicity, at doses that are maternally toxic.

**Breastfeeding**

Safety has not been established. Piperacillin is excreted in low concentrations in human milk; tazobactam concentrations in human milk have not been studied. Woman receiving TAZLIN 4,5 should not breastfeed their infants.

**Fertility**

TAZLIN 4,5 did not affect fertility in rats.

### 4.7 Effects on ability to drive and use machines

TAZLIN 4,5 is not known to affect ability to drive or operate machines.

### 4.8 Undesirable effects

**a. *Summary of the safety profile***

The most frequently reported adverse reactions are headache, diarrhoea, nausea, vomiting and abdominal pain.

**b. *Tabulated list of adverse reactions***

| System Organ Class | Adverse reaction | Frequency |
|---|---|---|
| **Infections and infestations** | Candidal superinfection, *Clostridium difficile* associated diarrhoea | Less frequent |
| **Blood and lymphatic system disorders** | Leucopenia, neutropenia, thrombocytopenia, anaemia, bleeding manifestations (including purpura, epistaxis, bleeding time prolonged), eosinophilia, haemolytic anaemia. Agranulocytosis, Coombs direct test positive, pancytopenia, prolonged partial | Frequency unknown |

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| | thromboplastin time, prothrombin time prolonged, thrombocytosis. | |
| **Immune system disorders** | Hypersensitivity reaction, anaphylactic/anaphylactoid reaction (including shock). | Less frequent |
| | Severe allergic reactions, including anaphylaxis, which may be associated with Kounis syndrome. | Frequency unknown |
| **Metabolism and nutrition disorders** | Hypoalbuminaemia, hypoglycaemia, hypoproteinaemia, hypokalaemia. | Frequency unknown |
| **Psychiatric disorders** | Insomnia | Frequency unknown |
| **Nervous system disorders** | Headache | Frequent |
| | Convulsions[1] | Frequency unknown |
| **Cardiac disorders** | Chest pain | Less frequent |
| | Kounis syndrome (allergic coronary artery spasm leading to myocardial ischemia) | Frequency unknown |
| **Vascular disorders** | Hypotension, phlebitis, thrombophlebitis | Less frequent |

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| | Flushing | Frequency unknown |
| **Gastro-intestinal disorders:** | Diarrhoea, nausea, vomiting, abdominal pain | Frequent |
| | Constipation, dyspepsia, stomatitis, pseudomembranous colitis (See section 4.4). | Frequency unknown |
| **Hepato-biliary disorders** | Alanine aminotransferase increased, aspartate aminotransferase increased, bilirubin increased, blood alkaline phosphatase increased, gamma-glutamyltransferase increased. | Less frequent |
| | Jaundice, hepatitis. | Frequency unknown |
| **Skin and subcutaneous tissue disorder** | Rash, pruritus, urticaria. | Less frequent |
| | Bullous dermatitis, erythema multiforme, Stevens-Johnson Syndrome, toxic epidermal necrolysis, Linear IgA bullous dermatosis (LABD) | Frequency unknown |
| **Musculoskeletal and connective tissue disorders** | Arthralgia, myalgia | Less frequent |

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| **Renal and urinary disorders** | Blood creatinine increased, interstitial nephritis, renal failure, increased blood urea | Frequency unknown |
| **General disorders and administration site conditions** | Fever, injection site reaction, rigors, chills, fever and rash in cystic fibrosis patients | Less frequent |

***c. Description of selected adverse reactions***

Unknown frequencies cannot be established from the available data.

[1] If high doses are given in patients with renal failure

***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 Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

**4.9 Overdose:**

**Symptoms of overdose**

See section 4.8. Patients may experience neuromuscular excitability or convulsions if higher than recommended doses are given intravenously (particularly in the presence of renal failure).

**Treatment of overdose**

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 medicines (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 TAZLIN 4,5 immediately. Start treatment with appropriate therapy such as oral teicoplanin or oral vancomycin and avoid medicines that inhibit peristalsis.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacological classification: A 20.1.1 Broad and medium spectrum antibiotics

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

ATC code: J01CR05

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

***Distribution***

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.

***Biotransformation***

Piperacillin is hepatically metabolized to the desethyl metabolite, which has minor activity and tazobactam is hepatically metabolised to a single, inactive metabolite.

***Elimination***

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

TAZLIN 4,5 does not contain excipients.

### 6.2 Incompatibilities

TAZLIN 4,5 should not be mixed with any other medicines in the same intravenous bag, bottle, or tubing as compatibility has not been established. Extemporaneous admixtures of TAZLIN 4,5 and aminoglycosides may result in substantial inactivation of the aminoglycoside. If these groups of antibacterials are administered concurrently, they should be administered at separate sites at least 1 hour apart.

Due to chemical instability, TAZLIN 4,5 should not be used in solutions containing sodium bicarbonate.

TAZLIN 4,5 should not be added to blood products or albumin hydrolysates.

### 6.3 Shelf life

2 years.

### 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.

### 6.5 Nature and contents of container

TAZLIN 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.

### 6.6 Special precautions for disposal

***Directions for reconstitution:***

Each bottle TAZLIN 4,5 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;
- 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 (e.g. 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

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**8 REGISTRATION NUMBER(S):**

42/20.1.1/0003

**9 DATE OF FIRST AUTHORISATION**

9 December 2008

**10 DATE OF REVISION OF THE TEXT**

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