SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TIGEBAX (Lyophilised cake/powder for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TIGEBAX: Each vial contains 50 mg of tigecycline. Contains sugar: 50 mg lactose monohydrate per 1 mL.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for Intravenous infusion.

Orange lyophilized cake/powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TIGEBAX is indicated for treatment of the following severe life-threatening infections in adults:

- Complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* group (includes *S. anginosus, S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes* and *Bacteroides fragilis*.
- Complicated intra-abdominal infections (cIAI) caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pnuemoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates only), *Staphylococcus aureus* (methicillin-susceptible isolates only), *Streptococcus anginosus* group (includes *S. anginosus*, *S. intermedius*, and

S. constellatus), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

4.2 Posology and method of administration

Posology:

Recommended Dosage:

The recommended dosage regimen for **TIGEBAX** is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of **TIGEBAX** should be administered over approximately 30-60 minutes every 12 hours.

The recommended duration of treatment with **TIGEBAX** for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5-14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

Method of administration:

Intravenous (IV) infusion.

Special Populations:

Patients with renal impairment:

No dosage adjustment of **TIGEBAX** is necessary in patients with renal impairment or in patients undergoing haemodialysis (see *section 5.1*).

Patients with hepatic impairment:

No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). Based on the pharmacokinetic profile of **TIGEBAX** in patients with severe hepatic impairment (Child Pugh C), the dose of **TIGEBAX** should be altered to 100 mg followed by 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (see *section 5.1*).

Paediatric patients:

Safety and effectiveness in patients under 18 years of age have not been established. Therefore, use in patients younger than 18 years old, is not recommended (see *section 4.4*).

Elderly patients:

No dosage adjustment is necessary in elderly patients (see *section 4.4*).

Race and gender:

No dosage adjustment is necessary based on race or gender (see *section 5.1*).

4.3 Contraindications

- Hypersensitivity to tigecycline or to any of the inactive ingredients of **TIGEBAX** (see *section 6.1*).
- Pregnancy and lactation.

4.4 Special warnings and precautions for use

In clinical studies in complicated skin and soft tissue infections (cSSTI), complicated intra-abdominal infections (cIAI), diabetic foot infections, nosocomial pneumonia and studies in resistant pathogens, a numerically higher mortality rate among tigecycline treated patients has been observed as compared to the comparator treatment. The causes of these findings remain unknown, but poorer efficacy and safety than the study comparators cannot be ruled out.

Anaphylaxis:

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial medicines, including tigecycline, as in **TIGEBAX**, and may be life-threatening.

Underlying disease:

Experience in the use of tigecycline for treatment of infections in patients with severe underlying diseases is limited.

Caution should be exercised when considering **TIGEBAX** monotherapy in patients with cIAI secondary to clinically apparent intestinal perforation. In Phase III cIAI studies (n=1642), six patients treated with **TIGEBAX** and two patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The six patients treated with **TIGEBAX** had higher APACHE II scores (median=13) vs the two patients treated with imipenem/cilastatin (APACHE II scores=4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

In clinical trials in cSSTI, the most common type of infection in **TIGEBAX**-treated patients was cellulitis (58,6 %), followed by major abscesses (24,9 %). Patients with severe underlying disease, such as those that were immunocompromised, patients with decubitus ulcer infections, or patients that had infections requiring longer than 14 days of treatment (for example, necrotizing fasciitis), were not enrolled. A limited number of patients were enrolled with co-morbid factors such as diabetes (25,8 %), peripheral vascular disease (10,4 %), intravenous substance abuse (4,0 %), and HIV-positive infection (1,2 %). Limited experience is also available in treating patients with concurrent bacteraemia (3,4 %). Therefore, caution is advised when treating such patients. The results in a large study in patients with diabetic foot infection, showed that **TIGEBAX** was less effective than comparator, therefore, **TIGEBAX** is not recommended for use in these patients (see *section 4.1*).

In clinical trials in cIAI, the most common type of infection in **TIGEBAX**-treated patients was complicated appendicitis (50,3 %), followed by other diagnoses less commonly reported such as complicated cholecystitis (9,6 %), perforation of intestine (9,6 %), intra-abdominal abscess (8,7 %), gastric or duodenal ulcer perforation (8,3 %), peritonitis (6,2 %) and complicated diverticulitis (6,0 %). Of these patients, 77,8 % had surgically apparent peritonitis. There were a limited number of patients with severe underlying disease such as immunocompromised patients, patients with APACHE II scores > 15 (3,3 %), or with surgically apparent multiple intra-abdominal abscesses (11,4 %). Limited experience is also available in treating patients with concurrent bacteraemia (5,6 %). Therefore, caution is advised when treating such patients.

Consideration should be given to the use of combination antibacterial therapy whenever tigecycline is to be administered to severely ill patients with cIAI secondary to clinically apparent intestinal perforation or patients with incipient sepsis or septic shock (see *section 4.8*).

The effect of cholestasis in the pharmacokinetics of **TIGEBAX** has not been properly established. Biliary excretion accounts for approximately 50 % of the total tigecycline excretion. Therefore, patients presenting with cholestasis should be closely monitored.

Prothrombin time or other suitable anticoagulation test should be used to monitor patients if **TIGEBAX** is administered with anticoagulants (see *section 4.5*).

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including **TIGEBAX** and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea during or subsequent to the administration of any antibacterial medicines (see *section 4.8*).

Results of studies in rats with **TIGEBAX** have shown bone discolouration. **TIGEBAX** may be associated with permanent tooth discolouration in humans if used during tooth development (see *section 4.8*).

Hepatic dysfunction and hepatic failure:

Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with **TIGEBAX**.

Cases of liver injury with a predominantly cholestatic pattern have been reported in patients receiving **TIGEBAX** treatment, including some cases of hepatic failure with a fatal outcome. Although hepatic failure may occur in patients treated with **TIGEBAX** due to the underlying conditions or concomitant medicines, a possible contribution of **TIGEBAX** should be considered (see *section 4.8*).

Hospital acquired pneumonia:

The safety and efficacy of **TIGEBAX** in patients with hospital acquired pneumonia have not been established. In a study of patients with hospital acquired pneumonia, patients were randomised to receive **TIGEBAX** (100 mg initially; then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received **TIGEBAX** had lower cure rates (47,9 % versus 70,1 % for the clinically evaluable population) and greater mortality (25/131 (19,1 %) versus 14/122 (11,5 %)) than the comparator.

Superinfection:

The use of **TIGEBAX** may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

In clinical trials in cIAI patients, impaired healing of the surgical wound has been associated with superinfection.

A patient developing impaired healing should be monitored for the detection of superinfection. Patients who develop superinfections, in particular nosocomial pneumonia, appear to be associated with poorer outcomes. Patients should be closely monitored for the development of superinfection. If a focus of infection other than complicated skin and soft structure infections or cIAI is identified after initiation of **TIGEBAX** therapy, consideration should be given to instituting alternative antibacterial therapy that has been demonstrated to be efficacious in the treatment of the specific type of infection(s) present.

Tetracycline class antibiotics:

Glycylcycline class antibiotics are structurally similar to tetracycline class antibiotics and may have similar adverse effects. Such effects may include photosensitivity, pseudotumour cerebri and anti-anabolic action (which has led to increased blood urea, uremia, acidosis and hyperphosphataemia). Therefore, **TIGEBAX** should be administered with caution in patients with known hypersensitivity to tetracycline class antibiotics. Results of studies in rats with **TIGEBAX** have shown bone

discolouration. **TIGEBAX** may be associated with permanent tooth discolouration in the teeth in humans during tooth development.

Pancreatitis:

As with tetracycline, pancreatitis has been reported with the use of **TIGEBAX**.

Acute pancreatitis, which can be serious, has occurred in association with **TIGEBAX** treatment. The diagnosis of acute pancreatitis should be considered in patients taking **TIGEBAX** who develop clinical symptoms, signs, or laboratory abnormalities suggestive of acute pancreatitis. Most of the reported cases developed after at least one week of treatment. Cases have been reported in patients without known risk factors for pancreatitis. Patients usually improve after **TIGEBAX** discontinuation. Consideration should be given to the cessation of **TIGEBAX** in cases suspected of having developed pancreatitis.

Paediatric population:

Safety and efficacy in patients under the age of 18 years have not been established. **TIGEBAX** is not recommended for use in patients under the age of 18 years (see *section 4.2*).

TIGEBAX should not be used in children under 8 years of age due to the lack of safety and efficacy data in this age group and because **TIGEBAX** may be associated with permanent teeth discolouration (see *sections 4.2* and *4.8*).

Elderly population:

No unexpected overall differences in safety or effectiveness are expected in the elderly population, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

Prescribers should adhere to the principles of antibiotic stewardship.

4.5 Interaction with other medicines and other forms of interaction

TIGEBAX (100 mg followed by 50 mg every 12 hours) and digoxin (0,5 mg followed by 0,25 mg every 24 hours) were co-administered to healthy subjects in a drug interaction study. **TIGEBAX** slightly

decreased the C_{max} of digoxin by 13 % but did not affect the AUC or clearance of digoxin. This small change in C_{max} did not affect the steady state pharmacodynamic effects of digoxin as measured by changes in ECG intervals. In addition, digoxin did not affect the pharmacokinetic profile of **TIGEBAX**. Therefore, no dosage adjustment is necessary when **TIGEBAX** is administered with digoxin.

Concomitant administration of **TIGEBAX** (100 mg followed by 50 mg every 12 hours) and warfarin (25 mg single dose) to healthy subjects resulted in a decrease in clearance of R-warfarin and S-warfarin by 40 % and 23 %, and an increase in AUC by 68 % and 29 %, respectively. The mechanism of this interaction is still unclear. **TIGEBAX** did not significantly alter the effects of warfarin on increased international normalized ratio (INR). In addition, warfarin did not affect the pharmacokinetic profile of **TIGEBAX**. However, prothrombin time or other suitable anticoagulation test should be monitored if **TIGEBAX** is administered with warfarin, since tigecycline may prolong the prothrombin time (PT) and activated partial thromboplastin time (aPTT).

In vitro studies in human liver, microsomes indicate that **TIGEBAX** does not inhibit metabolism mediated by any of the following 6 cytochrome CYP 450 isoforms: 1A2,2C8, 2C9,2C19, 2D6, and 3A4.

In vitro, tigecycline is neither a competitive inhibitor nor an irreversible inhibitor of CYP450 enzymes. Therefore, **TIGEBAX** is not expected to alter the metabolism of drugs metabolised by these enzymes. In addition, because **TIGEBAX** is not extensively metabolised, clearance of **TIGEBAX** is not expected to be affected by drugs that inhibit or induce the activity of these CYP450 isoforms.

In *in vitro* studies, no antagonism has been observed between **TIGEBAX** and other commonly used antibiotic classes.

Based on an *in vitro* study tigecycline is a P-gp substrate. Co-administration of P-gp inhibitors (e.g., ketoconazole or ciclosporin) or P-gp inducers (e.g., rifampicin) could affect the pharmacokinetics of **TIGEBAX**.

Concurrent use of antibiotics with oral contraceptives may render oral contraceptives less effective.

Interference with laboratory and other diagnostic tests:

There are no reported drug laboratory test interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy:

TIGEBAX may cause foetal harm when administered in pregnant women. There are no adequate and well-controlled studies of **TIGEBAX** in pregnant women. Studies in animals have shown that **TIGEBAX** crossed the placenta and is found in foetal tissues. The potential risk for humans is unknown.

TIGEBAX should not be used in pregnant women (see *section 4.3*).

Tetracycline class antibiotics, **TIGEBAX** may also induce permanent dental defects (discolouration and enamel defects) and a delay in ossification processes in foetuses, exposed *in utero* during the last half of gestation, and in children under eight years of age due to the enrichment in tissues with a high calcium turnover and formation of calcium chelate complexes (see *section 4.4*). **TIGEBAX** is contraindicated in pregnancy (see *section 4.3*).

TIGEBAX has not been studied for use during labour and delivery.

Lactation:

It is unknown whether **TIGEBAX** is excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of **TIGEBAX** in milk. A risk to the newborns/infants cannot be excluded (see *section 4.3*). The use of **TIGEBAX** is contraindicated in breastfeeding.

Fertility:

TIGEBAX did not affect mating or fertility in rats at exposures up to 4,7 times the human daily dose based on the area under the curve (AUC). In female rats, there were no medicine-related effects on ovaries or oestrus cycles at exposures up to 4,7 times the human daily dose based on AUC.

4.7 Effects on ability to drive and use machines

TIGEBAX may cause side effects, such as dizziness which may impair the ability to drive an operate machinery. Caution is advised before driving a vehicle or operating machinery until the effects of **TIGEBAX** are known.

4.8 Undesirable effects

a. Summary of the safety profile

In clinical trials, the most common medicinal product-related treatment emergent adverse reactions were reversible nausea and vomiting, which usually occurred early (on treatment days 1-2) and were generally mild or moderate in severity. Adverse reactions reported with tigecycline, including clinical trials and post-marketing experience, are tabulated below.

b. Tabulated list of adverse reactions

MedDRA SOC	**Frequency**	**Adverse events**
Infections and infestations	Frequent	sepsis/septic shock, pneumonia, abscess, infections
Blood and lymphatic system disorders	Frequent	prolonged activated partial thromboplastin time (aPTT), prolonged prothrombin time (PT)
	Less frequent	thrombocytopenia, increased international normalised ratio (INR)
	Frequency unknown	hypofibrinogenemia, anaemia, leucocytosis
Immune system disorders	Frequency unknown	anaphylaxis/anaphylactoid reactions
Metabolism and nutrition disorders	Frequent	hypoglycaemia, hypoproteinaemia
	Less frequent	hyponatraemia
Nervous system disorders	Frequent	dizziness
Vascular disorders	Frequent	phlebitis

	Less frequent	thrombophlebitis
Gastrointestinal disorders	Frequent	nausea, vomiting, diarrhoea
	Frequent	abdominal pain, dyspepsia, anorexia
	Less frequent	acute pancreatitis
Hepatobiliary disorders	Frequent	elevated aspartame aminotransferase (AST) in serum, elevated alanine aminotransferase (ALT) in serum, hyperbilirubinaemia
	Less frequent	jaundice, liver injury, hepatic cholestasis
	Frequency unknown	hepatic failure
Skin and subcutaneous tissue disorders	Frequent	pruritis, rash
	Frequency unknown	severe skin reactions, including Stevens-Johnson Syndrome
General disorders and administration site disorders	Frequent	impaired healing, injection site reaction, headache
	Less frequent	injection site inflammation, injection site pain, injection site oedema injection site phlebitis
Investigations	Frequent	elevated amylase in serum, increased blood urea

Description of selected adverse reactions

In Phase 3 double blind studies that included a comparator and employed a 1:1 randomisation, death occurred in 4,7 % (107/2274) of patients receiving **TIGEBAX** and 3,8 % (85/2264) of patients receiving comparator drugs. In a pooled analysis of these studies, the risk difference of all-cause mortality was 1,0 % (95 % CI-0,3; 2,2) between **TIGEBAX** and comparator treated patients. No significant differences were observed between treatments by infection type (see table below). Generally, deaths represented complications of the underlying disease or progression of disease. A causal relationship to **TIGEBAX** has not been established.

The most common drug-related treatment emergent adverse events, in patients treated with **TIGEBAX** were nausea 20,4 % (12,9 % mild; 6,6 % moderate; 0,8 % severe) and vomiting 13,5 %

(8,3 % mild; 4,5 % moderate; 0,6 % severe). In general, nausea or vomiting occurred early (days 1-2). Discontinuation from **TIGEBAX** was most frequently associated with nausea (1,3 %) and vomiting (1,0 %).

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. Health care 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

No specific information is available on the treatment of overdosage.
Intravenous administration of **TIGEBAX** at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting.
TIGEBAX is not removed in significant quantities by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Mechanism of action

Tigecycline is a glycylcycline antibiotic and inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains.
Tigecycline is considered to be bacteriostatic.

The information below provides only approximate guidance on the probability as to whether the microorganism will be susceptible to tigecycline or not:

Commonly susceptible species

Gram-positive aerobes:

- *Enterococcus* faecalis* (includes vancomycin-susceptible strains)
- *Staphylococcus aureus** (includes methicillin-susceptible and-resistant strains, including isolates that bear molecular and virulence markers commonly associated with community acquired MRSA including the SCCmec type IV element and the pvl gene)
- *Streptococcus agalactiae**
- *Streptococcus anginosus* group* (includes *S. anginosus, S. intermedius* and *S. constellatus*)
- *Streptococcus pyogenes**

Gram-negative aerobes:

- *Citrobacter freundii**
- *Escherichia coli**
- *Klebsiella oxytoca**
- *Enterobacter cloacae**
- *Klebsiella pneumoniae**

Anaerobes:

- *Bacteroides fragilis**
- *Bacteroides thetaiotaomicron**
- *Bacteroides uniformis**
- *Bacteroides vulgatus**
- *Clostridium perfringens**
- *Peptostreptococcus micros**

*Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters of tigecycline are summarised in the table below. IV infusions of tigecycline should be administered over approximately 30-60 minutes.

	Single dose **100 mg**	**Multiple dose[c]** **50 mg q12h**
C_{max} (µg/mL)[a]	1,45 (22 %)	0,87 (27 %)
C_{max} (µg/mL)[b]	0,90 (30 %)	0,63 (15 %)
AUC (µg-h/mL)	5,19 (36 %)	-
AUC_{0-24h} (µg-h/mL)	-	4,70 (36 %)
C_{min} (µg/mL)	-	0,13 (59 %)
$t_{1/2}$ (h)	27,1 (53 %)	42,4 (83 %)
CL (L/h)	21,8 (40 %)	23,8 (33 %)
CL_r (mL/min)	38,0 (82 %)	51,0 (58 %)
V_{s8} (L)	568 (43 %)	639 (48 %)

[a] 30-minute infusion

[b] 60-minute infusion

[c] 100 mg initially, followed by 50 mg every 12 hours

Absorption:

Tigecycline is administered intravenously and therefore has 100 % bioavailability.

Distribution:

The *in vitro* plasma protein binding of tigecycline ranges from approximately 71 %-89 % at concentrations observed in clinical studies (0,1-1,0 µg/mL). Animal and human pharmacokinetic studies have demonstrated that tigecycline readily distributes to tissues.

In rats receiving single or multiple doses of ^{14}C-tigecycline, radioactivity was well distributed to most tissues, with the highest overall exposure observed in bone, bone marrow, thyroid gland, spleen, kidney and salivary glands. In humans, the steady-state volume of distribution of tigecycline averaged 500-700 L (7-9 L/kg), indicating that tigecycline is extensively distributed beyond the plasma volume and concentrates into tissues of humans.

Two studies examined the steady-state pharmacokinetic profile of tigecycline in specific tissues or fluids of healthy subjects receiving tigecycline 100 mg followed by 50 mg every 12 hours. In a bronchoalveolar lavage study, the tigecycline AUC_{0-12h} (134 µg.h/mL) in alveolar cells was approximately 77,5-fold higher than the AUC_{0-12h} in the serum of these subjects, and the AUC_{0-12h} (2,28 µg.h/mL) in epithelial lining fluid was approximately 32 % higher than the AUC_{0-12h} in serum. In a skin blister study, the AUC_{0-12h} (1,61 µg.h/mL) of tigecycline in skin blister fluid was approximately 26 % lower than the AUC_{0-12h} in the serum of these subjects.

In a single-dose study, tigecycline 100 mg was administered to subjects prior to undergoing elective surgery or medical procedure for tissue extraction. Tissue concentrations at 4 hours after tigecycline administration were measured in the following tissue and fluid samples: gallbladder, lung, colon, synovial fluid and bone. Tigecycline attained higher concentrations is tissues versus serum in gallbladder (38-fold, n=6), lung (8,6-fold, n=1) and colon (2,1-fold, n=5). The concentration of tigecycline in these tissues after multiple doses has not been studied.

Metabolism:

Tigecycline is not extensively metabolised. *In vitro* studies with tigecycline using human liver microsomes, liver slices and hepatocytes led to the formation of only trace amounts of metabolites. In healthy male volunteers, receiving, ^{14}C-tigecycline, tigecycline was the primary ^{14}C-labelled material recovered in urine and faeces, but a glucuronide, an N-acetyl metabolite and a tigecycline epimer (each at no more than 10 % of the administered dose) were also present.

Elimination:

The recovery of the total radioactivity in faeces and urine following administration of ^{14}C-tigecycline indicates that 59 % of the dose is eliminated by biliary/faecal excretion, and 33 % is excreted in urine. Overall, the primary route of elimination for tigecycline is biliary excretion of unchanged tigecycline. Glucuronidation and renal excretion of unchanged tigecycline are secondary routes.

Special populations:

Hepatic impairment:

In a study comparing 10 patients with mild hepatic impairment (Child Pugh A),10 patients with moderate hepatic impairment (Child Pugh B), and five patients with severe hepatic impairment (Child Pugh C) to 23 age and weight-matched healthy control subjects, the single-dose pharmacokinetic disposition of tigecycline was not altered in patients with mild hepatic impairment. However, systemic clearance of tigecycline was reduced by 25 %, and the half-life of tigecycline was prolonged by 23 % in patients with moderate hepatic impairment (Child Pugh B). In addition, systemic clearance of tigecycline was reduced by 55 %, and half-life of tigecycline was prolonged by 43 % in patients with severe hepatic impairment (Child Pugh C).

Based on the pharmacokinetic profile of tigecycline, no dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). However, in patients with severe hepatic impairment (Child Pugh C), the dose of tigecycline should be reduced to 100 mg followed by 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response (see *section 4.2*).

Renal impairment:

A single-dose study compared six subjects with severe renal impairment (creatinine clearance Cl_{Cr} 30 mL/min), four end stage renal disease patients receiving tigecycline 2 hours before haemodialysis, four end stage renal disease patients receiving tigecycline after haemodialysis, and six healthy control subjects. The pharmacokinetic profile of tigecycline was not altered in any of the renally impaired patient groups, nor was tigecycline removed by haemodialysis. No dosage adjustment of tigecycline is necessary in patients with renal impairment or in patients undergoing haemodialysis (see *section 4.2*).

Elderly:

No overall differences in pharmacokinetics were observed between healthy elderly subjects (n=15, age 65-75; n=13, age >75, and younger subjects (n=18) receiving a single, 100 mg dose of tigecycline. Therefore, no dosage adjustment is necessary based on age.

Children:

The pharmacokinetics of tigecycline in patients less than 18 years of age have not been established.

Gender:

In a pooled analysis of 38 women and 298 men participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance between women (20,7±6,5 L/h) and men (22,8±8,7 L/h). Therefore, no dosage adjustment is necessary based on gender.

Race:

In a pooled analysis of 73 Asian subjects, 53 Black subjects,15 Hispanic subjects, 190 White subjects and 3 subjects classified as “other” participating in clinical pharmacology studies, there was no significant difference in the mean (±SD) tigecycline clearance among the Asian subjects (28,8±8,8 L/h), Black subjects (23,0±7,8 L/h), Hispanic subjects (24,3±6,5 L/h), White subjects (22,1±8,9 L/h), and “other” subjects (25,0±4,8 L/h). Therefore, no dosage adjustment is necessary based on race.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid, lactose monohydrate, sodium hydroxide, tigecycline, water for injection.

6.2 Incompatibilities

The following active substances should not be administered simultaneously through the same Y-site as tigecycline: Amphotericin B, amphotericin B lipid complex, diazepam, esomeprazole, omeprazole and intravenous solutions that could result in an increase of pH above 7 (see *section 4.2*).

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

24 months

Once reconstituted and diluted in the bag or other suitable infusion container (e.g. glass bottle), **TIGEBAX** should be used within 48 hours when stored at 2-8 °C or 24 hours when stored at 25 °C.

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

TIGEBAX:

5 mL USP type I clear glass lyo vial, stopper with 13 mm ready to sterilize rubber stopper and sealed with 13 mm aluminum flip-off seals.

6.6 Special precautions for disposal and other handling

The lyophilised powder should be reconstituted with 5,3 mL of 0,9 % sodium chloride injection, USP, or 5 % dextrose injection, USP or lactated ringer's solution to achieve a concentration of 10 mg/mL of **TIGEBAX**.

The vial should be gently swirled until the drug dissolves. Thereafter, 5 mL of the reconstituted solution should be immediately withdrawn from the vial and added to a 100 mL IV bag for infusion.
For a 100 mg dose, reconstitute using two vials into a 100 mL IV bag. (Note: The vial contains a 6 % overage. Thus, 5 mL of reconstituted solution is equivalent to 50 mg of the drug).

The reconstituted solution should be yellow to orange in colour: if not, the solution should be discarded. Parenteral drug products should be inspected visually for particulate matter and discolouration (e.g., green or black) prior to administration whenever solution and container permit. Once reconstituted, **TIGEBAX** may be stored at room temperature for up to 24 hours (up to 6 hours in the vial and the remaining time in the IV bag).

Alternatively, **TIGEBAX** mixed with 0,9 % sodium chloride injection, USP or 5 % dextrose injection, USP, may be stored refrigerated at 2 °C-8 °C for up to 48 hours following immediate transfer of the reconstituted solution into the IV bag.

TIGEBAX may be administered intravenously through a dedicated line through a Y-site. If the same IV line is used for sequential infusion of several medicines, the line should be flushed before and after infusion of **TIGEBAX** with either 0,9 % sodium chloride injection or 5 % dextrose injection. Injection should be made with an infusion solution compatible with **TIGEBAX** and with any other medicine(s) administered via this common line.

Compatibilities, incompatibilities and handling:
Compatible intravenous solutions include 0,9 % sodium chloride injection, USP, 5 % dextrose injection, USP and lactated ringer's injection, USP.

TIGEBAX is compatible with the following medicines or diluents when used with either 0,9 % sodium chloride injection of 5 % dextrose injection and administered simultaneously through the same line as amikacin, dobutamine, dopamine HCl, gentamycin, haloperidol, lactated ringer's, lidocaine (lignocaine) HCl, morphine, noradrenalin (norepinephrine), piperacillin/tazobactam (EDTA formulation), potassium chloride, propofol, ranitidine HCl, theophylline and tobramycin.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Glenmark Pharmaceuticals South Africa (Pty) Ltd

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