SCHEDULING STATUS: S4

S1

PROPRIETARY NAMES AND DOSAGE FORMS:

TARGOCID® 200 (powder for solution for injection/infusion or oral solution)

TARGOCID® 400 (powder for solution for injection/infusion)

TARGOCID® SOLVENT (water for injection)

COMPOSITION:

TARGOCID 200:

Per vial: Lyophilised teicoplanin 200 mg as teicoplanin sodium.

Sugar free.

TARGOCID 400:

Per vial: Lyophilised teicoplanin 400 mg as teicoplanin sodium.

Sugar free.

TARGOCID SOLVENT:

Per ampoule: Water for Injection 3 ml.

Reconstitute before use. The resultant solution is isotonic.

CATEGORY AND CLASS:

TARGOCID 200 and 400: A 20.1.1 Broad and medium spectrum antibiotics.

TARGOCID Solvent: A 32.4 Water for injection

PHARMACOLOGICAL ACTION:

Teicoplanin is a bactericidal, glycopeptide antibiotic, produced by fermentation of *Actinoplanes teicomyceticus*. It is active *in vitro* against both aerobic and anaerobic Gram-positive bacteria.

Bactericidal synergy has been demonstrated *in vitro*, in combination with aminoglycosides, against group D streptococci and staphylococci. *In vitro* combinations of teicoplanin with rifampicin or fluorinated quinolones show primarily additive effects and sometimes synergy. One-step resistance to teicoplanin could not be obtained *in vitro*, and multi-step resistance was only reached *in vitro* after 11 to 14 passages. Teicoplanin does not show cross-resistance with other classes of antibiotics. Following intravenous and intramuscular administration, teicoplanin is widely distributed in body tissues. It is slowly eliminated with a plasma half-life of 70 to 100 hours; the excretory route is renal. Teicoplanin is not absorbed when administered orally. Teicoplanin does not penetrate through the blood-brain barrier.

Species usually sensitive:

Staphylococcus aureus and coagulase negative staphylococci (sensitive or resistant to methicillin), streptococci, enterococci, *Listeria monocytogenes*, micrococci, group JK Corynebacteria, Gram-positive anaerobes including *Clostridium difficile* and peptococci.
In vitro sensitivity does not necessarily imply *in vivo* efficacy.

Species usually resistant:

Nocardia asteroides, Lactobacillus spp., Leuconostoc and all Gram-negative bacteria.

INDICATIONS:

TARGOCID is indicated in potentially serious Gram-positive infections, including those which cannot be treated with other antimicrobial medicines. The effectiveness of TARGOCID has been

documented in the following infections caused by organisms sensitive to TARGOCID: endocarditis, septicaemia and osteomyelitis, respiratory infections, skin and soft tissue infections, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis (CAPD).

TARGOCID may be used as prophylaxis in orthopaedic and vascular surgery at risk of Gram-positive infection.

TARGOCID 200 may be used orally for the treatment of antibiotic-associated diarrhoea, including pseudomembranous colitis, caused by *Clostridium difficile*.

CONTRAINDICATIONS:

Hypersensitivity to TARGOCID (see WARNINGS AND SPECIAL PRECAUTIONS).

Safety and efficacy have not been established in children under three years of age.

Pregnancy and lactation (see HUMAN REPRODUCTION).

TARGOCID must not be injected into the subarachnoid space (see WARNINGS AND SPECIAL PRECAUTIONS).

Renal insufficiency: Unless measurement of the serum concentrations can be guaranteed to accompany the therapy, patients with a creatinine clearance lower than or equal to 20 ml per minute must be excluded from therapy with TARGOCID.

WARNINGS AND SPECIAL PRECAUTIONS:

Hypersensitivity reactions:

Serious, life-threatening hypersensitivity reactions, sometimes fatal, have been reported with TARGOCID (e.g. anaphylactic shock). If an allergic reaction to TARGOCID occurs, treatment should be discontinued immediately and appropriate emergency measures should be initiated.

TARGOCID must be administered with caution in patients with known hypersensitivity to vancomycin, as cross-hypersensitivity reactions, including fatal anaphylactic shock, may occur.

However, a history of "Red Man Syndrome" with vancomycin, is not a contraindication to TARGOCID.

Infusion related reactions:

“Red Man Syndrome” (a complex of symptoms including pruritus, urticaria, erythema, angioneurotic oedema, tachycardia, hypotension, dyspnoea) has been rarely observed (even at the first dose). Stopping or slowing the infusion may result in cessation of these reactions. Infusion related reactions can be limited if the daily dose is not given via bolus injection but infused over a 30-minute period.

Severe bullous reactions:

Life-threatening or even fatal cutaneous reactions, Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) have been reported with the use of TARGOCID. If symptoms or signs of SJS or TEN (e.g. progressive skin rash, often with blisters or mucosal lesions) are present TARGOCID treatment should be discontinued immediately.

Thrombocytopenia:

Thrombocytopenia has been reported with TARGOCID, especially at doses higher than those usually recommended. It is advisable for periodic haematological studies to be performed during treatment.

Monitoring:

Hearing, haematologic, hepatic, and renal toxicities have been reported with TARGOCID. Appropriate monitoring of hearing, haematologic, liver, and renal function should be done, particularly in patients with renal insufficiency, patients receiving prolonged therapy, or patients who receive concurrent ototoxic or nephrotoxic medicines.

Serial renal and auditory function tests should be undertaken in the following circumstances:

- Prolonged treatment in patients with renal insufficiency: In patients with impaired kidney function the therapy should be monitored carefully. Where treatment in such patients is continued for longer than three weeks, regular checks are recommended on the serum level as well as on kidney, liver and auditory functions.
- Such tests are also recommended in cases of concurrent and sequential use of other medicines which may have neurotoxic and/or nephrotoxic properties. These include aminoglycosides, colistin, amphotericin B, ciclosporin, cisplatin, furosemide and ethacrynic acid (see INTERACTIONS).

However, there is no evidence of synergistic toxicity when TARGOCID is used in combination with the above medicines.

Route of administration:

TARGOCID may not be administered into the subarachnoid space (see CONTRAINDICATIONS).

TARGOCID should not be administered by intraventricular route, due to the risk of seizure.

Superinfection:

The use of TARGOCID, especially if prolonged, may result in overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Effects on ability to drive and use machines:

TARGOCID can cause dizziness and headache. The ability to drive or use machines may be affected. Patients experiencing these undesirable effects should not drive or use machines.

INTERACTIONS:

There is no record of any adverse interaction with other medication.

Due to the potential for increased adverse effects, TARGOCID should be administered with caution in patients receiving concurrent nephrotoxic or ototoxic medicines, such as aminoglycosides, amphotericin B, ciclosporin, and furosemide (see WARNINGS AND SPECIAL PRECAUTIONS).

HUMAN REPRODUCTION:

TARGOCID should not be used during pregnancy and breastfeeding, as safety has not been established. It is not known whether TARGOCID passes into breastmilk (see CONTRAINDICATIONS).

DOSAGE AND DIRECTIONS FOR USE:

The reconstituted TARGOCID injection may be administered either intravenously or intramuscularly. The intravenous injection may be administered either as a bolus or as a 30 minute infusion. Dosage is usually once daily but, in cases of severe infection, a second injection should be administered on the first day in order to reach the required serum concentration more rapidly.

The majority of patients with infections caused by organisms sensitive to the antibiotic, show a therapeutic response within 48 to 72 hours. The duration of therapy is determined by the type and severity of the infection and the clinical response of the patient. In endocarditis and osteomyelitis, treatment for three weeks or longer is recommended.

Determination of TARGOCID serum concentrations may optimise therapy. In severe infections, trough serum concentrations should not be less than 10 mg per litre. Peak concentrations measured one hour after a 400 mg intravenous dose are usually in the range of 20 to 50 mg per

litre; peak serum concentrations of up to 250 mg per litre have been reported after intravenous doses of 25 mg per kg body weight.

A relationship between serum concentration and toxicity has not been established.

THERAPEUTIC DOSAGE:

Adults and elderly patients with normal renal function:

Moderate infections:

Skin and soft tissue infections, urinary tract infections, lower respiratory tract infections

Loading dose:

- A single IV injection of 400 mg on the first day.

Maintenance dose:

- A single IV or IM injection of 200 mg daily.

Severe infections:

Joint and bone infections, septicaemia, endocarditis

Loading dose:

- 400 mg IV injection every 12 hours for the first three doses.

Maintenance dose:

- A single IV or IM injection of 400 mg daily.

In some clinical situations, such as infected, severely burned patients or *Staphylococcus aureus* endocarditis, unit maintenance doses of up to 12 mg per kg body weight may be required.

Note:

Standard doses of 200 mg and 400 mg are equivalent to mean doses of 3 mg per kg body weight and 6 mg per kg body weight respectively. In overweight patients it is recommended that the dose

be adapted to the weight of the patient as follows: moderate infections 3 mg per kg body weight; severe infections 6 mg per kg body weight.

Prophylaxis in orthopaedic and vascular surgery at risk of gram-positive infection:

400 mg intravenously as a single dose at induction of anaesthesia.

TARGOCID 200: Oral treatment of antibiotic-associated diarrhoea, including pseudomembranous colitis, caused by Clostridium difficile:

After reconstitution, the contents of the vial may be administered as an oral solution. The TARGOCID solution is tasteless.

Dosage: 200 mg orally twice a day for 10 days.

Children:

TARGOCID can be used to treat Gram-positive infections in children from the age of three years.

For ***severe*** infections and neutropenic patients, the recommended dose is 10 mg per kg body weight every 12 hours, by IV injection, for the first three doses. Thereafter a dose of 10 mg per kg body weight should be administered by either IV or IM injection as a single dose each day.

For ***moderate*** infections the recommended dose is 10 mg per kg body weight, by IV injection, every twelve hours for the first three doses. Thereafter a dose of 6 mg per kg body weight should be administered by either IV or IM injection as a single dose each day.

Adults and elderly patients with renal insufficiency:

For patients with impaired renal function, reduction of the dose is not required until the fourth day of treatment.

From the fourth day of treatment:

- *In mild renal insufficiency*:

Creatinine clearance between 40 ml and 60 ml per minute: the dose of TARGOCID should be halved, either by administering the initial unit dose every two days, or by administering half the initial unit dose once a day.

- *In severe renal insufficiency*:

Creatinine clearance less than 40 ml per minute and in haemodialysed patients: the dose of TARGOCID should be one third of the normal dose, either by administering the initial unit dose every third day, or by administering one third of the unit dose once a day.

TARGOCID is not removed by dialysis.

Unless measurement of the serum concentrations can be guaranteed to accompany the therapy, patients with a creatinine clearance lower than or equal to 20 ml per minute must be excluded from therapy with TARGOCID (see CONTRAINDICATIONS).

- *In continuous ambulatory peritoneal dialysis*:

After a single intravenous loading dose of 400 mg, if the patient is febrile, the recommended dosage is 20 mg per litre, per bag, in the first week, 20 mg per litre in alternate bags in the second week and 20 mg per litre in the overnight dwell bag only, in the third week.

TARGOCID is stable in peritoneal dialysis solutions (1,36 % or 3,86 % dextrose).

Do not keep mixed solutions for longer than 24 hours.

Monitoring the plasma concentrations:

If checks are carried out on the TARGOCID serum level in patients with severe infections, then the minimum serum level should not be below 10 mg per litre (measured just before the following dose).

Type of administration and duration of use:

1. Type of administration:

In order to produce the ready-to-use solution, all the TARGOCID SOLVENT (water for injection) in the accompanying ampoule is injected slowly into the vial with the dry substance. The vial is then rolled until the dry substance is completely dissolved. To avoid the formation of foam, **do not shake the vial**. If foam does develop during the preparation of the injection solution, it is recommended that the solution be left to stand for approximately 15 minutes until the foam has disappeared.

TARGOCID may be administered by either IV or IM injection. The IV dose may be given by rapid injection over one minute or by short infusion.

Following preparation of the ready-to-use solution, TARGOCID is injected directly intravenously or into the proximal end of a drip line after clamping the line. TARGOCID can be injected quickly, i.e. within one minute.

TARGOCID can also be injected intramuscularly.

For the purposes of infusion**,** TARGOCID is dissolved in 20 to 50 ml of infusion solution and administered over 20 to 30 minutes.

The following infusion solutions are suitable for mixing with TARGOCID:

- Isotonic saline solution 0,95 %
- Ringer's solution
- Ringer's lactate solution
- 5 % glucose solution
- Solutions containing 0,18 % sodium chloride and 4 % glucose.

Reconstituted solutions of TARGOCID should be used as soon as possible, otherwise they may be stored for 24 hours at 2 to 8 °C.

Incompatibilities:

TARGOCID and aminoglycosides are incompatible and should not be mixed in the same solution.

2. Duration of use:

With infections caused by TARGOCID-sensitive pathogens, a therapeutic result is shown in the majority of cases within 48 to 72 hours.

The duration of treatment is based upon the severity of the infection as well as upon the clinical and bacteriological progress. The treatment should be continued for at least three days after the patient has become afebrile and after the disappearance of clinical symptoms.

In cases of endocarditis or osteomyelitis, at least three weeks treatment is recommended.

TARGOCID should not be administered for longer than four months.

SIDE EFFECTS:

The following side effects have been observed and the frequencies have been indicated where known.

Infections and infestations:

Frequency unknown: superinfection (overgrowth of non-susceptible organisms)

Blood and lymphatic system disorders:

Less frequent: cases of reversible agranulocytosis, leucopenia, neutropenia, thrombocytopenia, eosinophilia

Immune system disorders (see WARNINGS AND SPECIAL PRECAUTIONS):

Less frequent: exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme, including Stevens-Johnson syndrome. In addition, infusion related events, called “Red Man Syndrome”

have been reported in which the events occurred without a history of previous TARGOCID exposure and did not recur on re-exposure when the infusion rate was slowed and/or the concentration decreased. These events were not specific to any concentration or rate of infusion

Frequency unknown: hypersensitivity reactions, rash, exanthema, pruritus, urticaria, fever, chills, rigors, bronchospasm, anaphylactic reactions, anaphylactic shock, angioedema, DRESS syndrome (medicine reaction with eosinophilia and systemic symptoms)

Nervous system disorders:

Less frequent: dizziness, headache, seizures

Ear and labyrinth disorders:

Frequency unknown: loss of hearing/deafness, tinnitus or vestibular disturbances have been observed in patients treated with TARGOCID in combination with a potentially ototoxic agent such as an aminoglycoside (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS)

Gastrointestinal disorders:

Less frequent: gastrointestinal disturbances, nausea, vomiting, diarrhoea

Hepato-biliary disorders:

Frequency unknown: increases in serum transaminases and/or serum alkaline phosphatase

Renal and urinary disorders:

Frequency unknown: a rise in serum creatinine, renal failure

General disorders and administration site conditions:

Frequency unknown: erythema, pain at the injection site, phlebitis, thrombophlebitis, injection site abscess with IM injection

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

General symptomatic measures are recommended for the management of an overdose. Available information on two children with agranulocytosis to whom several doses of 100 mg per kg body weight per day were administered in error, shows that despite very high serum concentrations of 300 mg per litre, no intoxication phenomena appeared.

TARGOCID is not removed by haemodialysis and only slowly by peritoneal dialysis.

IDENTIFICATION:

TARGOCID 200: A 10 ml clear glass vial with a light grey rubber stopper and a yellow flip-off top aluminium cap; containing a spongy, ivory-coloured, homogenous mass.

TARGOCID 400: A 20 ml clear, glass vial with a light grey rubber stopper and a green flip-off top aluminium cap; containing a spongy, ivory-coloured, homogenous mass.

TARGOCID SOLVENT: A clear glass ampoule, containing 3 ml of clear, colourless, odourless liquid.

Reconstituted product: Clear, yellowish solution.

PRESENTATION:

TARGOCID 200: 1 or 2 printed carton/s, each is containing a 10 ml labelled TARGOCID 200 vial together with a labelled TARGOCID SOLVENT ampoule and a leaflet.

TARGOCID 400: 1 printed carton containing a 20 ml labelled TARGOCID 400 vial together with a labelled TARGOCID SOLVENT ampoule and a leaflet.

STORAGE INSTRUCTIONS:

Store at or below 25 °C.

RECONSTITUTED PRODUCT: May be retained for 24 hours if stored at 2 C to 8 °C.

This product is for single use only, any unused portion should be discarded.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

TARGOCID® 200: Z/20.1.1/61

TARGOCID® 400: 32/20.1.1/0337

TARGOCID® SOLVENT: Z/34/159

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATES OF REGISTRATION:

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NAMIBIA

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BOTSWANA

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