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Goods
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COMMONWEALTH
DEPARTMENT OF
HEALTH, HOUSING,
LOCAL GOVERNMENT AND
COMMUNITY SERVICES

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FAX: DRUG EVALUATION
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PLEASE QUOTE APPL.NO:91.156.2
CO:7186
JEB/JEB

The Managing Director
Marion Merrell Dow Australia Pty Ltd
Unit 1, 25 Frenchs Forest Road East
FRENCHS FOREST NSW 2086

ATTENTION: REGULATORY AFFAIRS OFFICER

Dear Sir

Evaluation of data, submitted with your application dated 12 March 1991 on teicoplanin (Targocid) 100mg, 200mg and 400mg powder for injection has now been completed. A copy of the evaluation(s) - if not previously received - the Delegate's proposed action and an amended product information document (amendments to the product information may also be proposed by an evaluator and/or the Delegate) are enclosed herewith. The papers have been edited to delete unpublished Australian Drug Evaluation Committee (ADEC) deliberations and references to other sponsor's products, the names of evaluators, and confidential Government information.

You are requested to provide an original, plus one copy, of your comments on all the documents supplied. Your response is to be directed to: The Director, Drug Evaluation Branch (DEB) and clearly labelled **PRE-ADEC RESPONSE.** In view of the tight time schedule you may wish to seek an appointment with the relevant Delegate, **Dr Hari Arora**, to discuss the product information. The form of your response to the documents should be scientific comment upon those parts of the evaluation(s) and the Delegate's proposed action which you perceive to be erroneous or to contain unfair adverse commentary. Your response must be typed, legible, no longer than 5 single sided A4 pages, signed, dated, and without attachments. It must be based upon, and if necessary cross-referenced to, the data in your application. The Drug Evaluation Branch should be notified of potentially serious adverse effects which have been observed either for the first time or at a frequency which has become of concern since your application was made. Responses which do not meet these criteria will not be processed.

In addition to comments on the documents provided, please advise where relevant, the current status of the product in major foreign countries. Also please provide a current copy of product information approved for use in USA, Canada and Sweden. Foreign status should detail approvals (with indications), deferrals, withdrawals and rejections (with reasons for these three).

The evaluations and the Delegate's proposed action are to be considered at the 1993/6 (168) meeting of ADEC on 2-3 December 1993. You must ensure that status reports and any comments you wish to make on the documents provided are received by the Drug Evaluation Branch, in original, not facsimile form, by **9 November 1993.** This date is the absolute cut-off to allow timely processing of your application.

On receipt by the DEB of your comments, the original will be passed to the Delegate and the copy to the ADEC Secretariat. Comments received later will not be processed. If comments are not received by the cut-off date it will be assumed that you have no disagreement with the Delegate's proposed action. Please note that it is not essential that you provide comments; your application will still be considered at the nominated meeting of ADEC.

Your co-operation in resolving the outstanding issues at an early date will be appreciated.

Yours faithfully

[redacted]

for DIRECTOR
EVALUATION UNIT 2
DRUG EVALUATION BRANCH

27th October 1993.

COMPUTER UPDATED
ENTERED WTA: DEB
VERIFIED WTA:
C/No: 91.156.2. Date: 27/10/93

1992/6 ADEC
2-3 Dec 93

TEICOPLANIN (TARGOCID^{R}, MARION MERREL DOW) POWDER FOR INJECTION, 100MG, 200MG OR 400MG PER VIAL PLUS WATER FOR INJECTION

Application for Registration on the ARTG

Delegate's summary and comments:

1. Teicoplanin is an tetracyclic, glycopeptide antibiotic-complex produced by Actinoplanes teichomyceticus. It consists of six closely related glycopeptides of which five are designated as A-2 components. The sixth, designated A-3, is formed during purification and is less active on a weight basis. Chemically teichoplanin is related to vancomycin-ristocetin group of antibiotic (vancomycin is a tricyclic glycopeptide).

   Teichoplanin is proposed for the treatment of gram positive infections of the following organ systems (This includes patients allergic to beta lactam antibiotics or who have methicillin and cephalosporin resistant infection).

   Respiratory tract, Skin and soft tissue, Urinary tract Bone, Joints, Endocardium, Blood (septicaemia) Peritoneum (peritonitis associated with CAPD)

   Teichoplanin is also proposed for prophylaxis in patients in whom gram positive infection constitutes a hazard (eg cardiac, dental or orthopaedic surgery)

   It is proposed for use in all age groups.

   The proposed dose for treatment is 6-12 mg/kg IV (400-800 mg for adults) stat followed by 3-6 mg/kg IM or IV (200-400 mg for adults) daily as maintenance dose in mild to moderate infections (eg skin,soft tissues, urinary tract) except in patients with complicating illnesses (eg diabetes mellitus, cardiovascular disease etc) where 6 mg/kg/day is recommended. In moderate infections (septicaemia/bacteraemia, acute or chronic osteomyelitis) two initial doses of 6-12 mg/kg (12 hrs apart) IV are to be followed by 6 mg/kg/day (?? IV or IM). For moderate to severe infections: for septic arthritis 12 mg/kg/12 h 3 doses, then 12 mg/kg/day; Streptococcal endocarditis: 6-12 mg/kg/12 h on day 1 followed by 6-12 mg/kg/day; Staph aureus endocarditis: 30 mg/kg/12 h on day 1 followed by 30 mg/kg/day.

   Proposed treatment durations are : for superficial infections 1-2 weeks, for uncomplicated bacteraemia 2-4 weeks and for endocarditis, osteomyelitis and septic arthritis 3-6 weeks. In patients with impaired renal function dose is proposed to be adjusted after four days.

For prophylaxis one to three doses of 400 mg each are proposed.

2. Chemistry and quality control:

All C&QC matters have been resolved with the sponsor except for revision of bacterial endotoxin test methods. These are under negotiation with the sponsor but evaluator does not consider that it need delay progress of application to the Committee.

3. Animal toxicology:

Evaluator has not objected to registration but has expressed some reservations about the quality of submitted data. Some comments in the evaluation report, which may have clinical significance, are drawn to the Committee's attention hereunder.

i) In vivo efficacy in animals was demonstrated only against infections due to MRSA, Strep pyogenes and Strep pneumoniae.
ii) Major toxicity studies used subcutaneous injection but kinetic data for this route were not provided. Hence, toxicity profile of teicoplanin, for the proposed route of administration (IV/IM) was not adequately established.
iii) Kidneys were the primary target organ for toxicity in animals. In rats teicoplanin and vancomycin, given subcutaneously, were equally nephrotoxic.
iv) Although teicoplanin is proposed for use in children no toxicology studies were conducted in young animals.

4. Bioavailability and human pharmacokinetics:

4.1 Bioavailability following IM injection:

An intramuscular injection of 6 mg/kg (dissolved in saline?) was 100% bioavailable. No data were provided concerning bioavailability following reconstitution with lidocaine.

4.2 Human pharmacokinetics:

Young healthy adults: 3 mg/kg or 200 mg single dose:

	IV	IM
Cmax	variable, depending on speed of injection; On completion of distribution phase (3 h) plasma levels same as after IM injection	7.12 µg/ml
AUC0-∞mg.h/L	576	645

Tmax	at end of injection	4.1 h
$T_{½}$	70 - 100 h	
V_d	0.68-0.83 L/kg	
Protein binding	Approx 90%	

Following IM injection of 3 mg/kg (6 doses over 5 days; first 3 doses 12 hourly) trough levels on day 5 were 5.4-7.3 μg/ml (suggesting cumulation; Cmax on day 1 was 7.1 μg/ml whereas on day 5 it was 12.1 μg/ml)

No information on kinetics of 6 mg/kg IM. Information on 6 mg/kg (800 mg) IV single dose was limited but suggests kinetics similar to 3 mg/kg IV single dose.

Information on multiple doses inadequate.

Impaired renal function:

Crcl	< 60ml/min	$t_{½}$ & AUC prolonged almost 50%
	< 10 ml/min	$t_{½}$ & AUC nearly doubled
V_d	unchanged	

CAPD or haemodialysis did not affect kinetics

Elderly patients: (mean Crcl <51.3 ml/min)

Dose 6 mg/kg; data limited; suggestive of higher AUC and prolonged $t_{½}$.

Children:

Data inadequate; no information on plasma concentration; $t_{½}$ in boys (2-13 yrs age) 58.2 h; girls (4-12 yrs age) 20.4 h; neonates (full term) 30.3 h.

Tissue penetration:

Poor penetration into CSF, peritoneal fluid, subcutaneous fat, and RBC. Levels in bone and plasma similar (approx 7 μg/ml after 3 mg/kg). Levels in joint fluid, lungs were lower (around 4 μg/ml). Data concerning levels in pleural fluid inadequate but suggest some penetration.

No data on:

i) kinetics in patients with impaired hepatic function;
ii)metabolism, urinary concentrations or drug interactions.

5. Clinical studies:

5.1 Microbiology:

Almost all isolates Staph aureus (methicillin sensitive/resistant), Staph epidermidis, a few other staphs, some streptococci or a few enterococci. Claimed clinical efficacy against all gram positive infections is, thus, not supported by data.

5.2 Clinical safety:

Trials were generally poor in design and/or execution and data collection less than satisfactory (in some cases probably due to the type of population studied). It is unclear from the clinical evaluation report whether teicoplanin was given as a bolus or as slow infusion in the reported studies. The largest coherent study was in patients with bone/joint infections in which 342 patients appear to have been assessed for safety. Approx 17% discontinued due to adverse drug reactions (ADR). Teicoplanin caused hypersensitivity reactions in approx 28% cases; there were also instances of hepatic, renal and ototoxicity as well as haematological toxicity. Comparative ADR data against vancomycin do not appear to have been gathered. Hence, there is no evidence to show that teicoplanin is any safer than vancomycin. Toxicity profiles appears to be qualitatively similar to vancomycin.

5.2 Clinical Efficacy:

5.2.1 Endocarditis: Data: Two pivotal studies; one non-pivotal study.
Pivotal studies: i) Study 102-013: open, non-comparative; 31 evaluable patients; Dose: IV; Varied during the course of the trial; initiated at 6 mg/kg 12 hourly for 3 doses then 3-6 mg/kg 12 hourly; later increased to 30 mg/kg, three doses 12 hrly at start, then 15 mg/kg 12 hourly for Staph endocarditis and 6-15 mg/kg/day for non-Staph endocarditis; Duration (Usual?) 4-6 weeks; maximum 10 weeks. 20/31 cured or improved; Of 11 failures 9 due to Staphylococci 2 due to Streptococci.
ii) Study 102-014: double blind, randomised, comparative against vancomycin; 14 evaluable on Teicoplanin; Dose: IV; Varied during trial; initially 6 mg/kg 12 hourly for 3 doses then 6 mg/kg/day IV; later increased to a maximum of 30 mg/kg/day; Duration: 3-4 weeks. Cured/improved teicoplanin 3/14 (21%), Vancomycin 5/6 (83%)

Non-pivotal study:(102-019; Appendix 7) This study provided for follow up; efficacy for teicoplanin (56%) was lower than vancomycin (88%); trough levels aimed were 40-60 μg/ml teicoplanin (higher than in proposed product information)

Comments:

The open pivotal study appears to have no provision for proper follow up; double blind pivotal study and non-pivotal study (both with provision for follow up) indicate lower efficacy for teicoplanin. Both pivotal studies combined dose finding with efficacy. Separate efficacy analysis, for the various doses used in the studies, was not provided (although lower doses are stated to be ineffective). Optimum dose, thus, has not been established. Trialists aimed to achieve/maintain teicoplanin trough plasma levels at 20, 25 or 40-60 μg/ml. No kinetic data were provided on dosage regimens which will attain/maintain these trough levels. No data provided on use in vancomycin resistant/intolerant patients.

5.2.2 Skin and soft tissue infections: Data: One pivotal and two non-pivotal studies.

Pivotal study: Study 102-007: randomised, comparative arm against cefazolin, and a non-randomised arm; Initial dose 6 mg/kg loading followed by 3 mg/kg/day; later doubled. Ninety percent of patients were on concomitant antibiotics for gram negative/anaerobic cover (most commonly metronidazole or aztreonam but also others).

Randomised arm: 44/50 (88%) cured/improved with 3 mg/kg/day IM teicoplanin; 30/32 (94%) on 6 mg/kg/day. With IV teicoplanin 63/66 (95%) cured/improved on 3 mg/kg/day and 38/39 (97%) on 6 mg/kg/day.
Non-randomised arm: 138/151 (91%) were cured or improved on 3 mg/kg/day and 30/30 (100%) on 6 mg/kg/day.

Non-pivotal studies: i) Study 86/12/1: (Appendix 9) MRSA infections (mainly cellulitis), using 6 mg/kg/12 hrly for 3 doses and then 6 mg/kg/day for 10-14 days showed teicoplanin to be as effective (86%) as vancomycin (97.6%).
ii) Study 102-001 & 002: (Appendix 8) included some skin and soft tissue infections amongst a mixed bag of infections; only overall cure/improvement rates were cited in evaluation report. Efficacy for individual infections (eg skin/soft tissues etc) not assessable.

Comments:

Teicoplanin was not used as monotherapy in the pivotal study and it appears that there were many cases with mixed infections whose individual roles remain undefined. Information concerning use of combination therapy in non-pivotal studies is unclear. Pivotal study was designed as a dose finding cum phase 3 efficacy trial with changing dosage regimens during the trial. Appropriate dose remains undefined. Efficacy analysis of various doses was not provided and bases for using high or low doses are unclear. IM and IV routes appeared to be equally effective in this trial. Proportion of MRSA isolates was not stated (except in the non-pivotal study 86/12/1 on MRSA infections). No data on efficacy in patients with vancomycin resistance/intolerance.

5.2.3 Bone and joint infections: Data: One pivotal study; two non-pivotal studies.

Pivotal study: Study 102-012: Dose variable (see Appendix 6); Duration: osteomyelitis 6 weeks; septic arthritis 4 weeks;

Osteomyelitis: Of 90 cases of acute and 79 of chronic osteomyelitis cure/improvement occurred in 90 and 89% cases respectively irrespective of dosage regimen.

Septic arthritis: response rate was poor with 6 mg/kg/day dose but improved to 94% with 12 mg/kg/day. Numbers on each dosage regimen not stated.

Non-pivotal studies: Studies 102-001 &002 and 86/12/1: Some patients with osteomyelitis or bone/joint infection but data not analysed separately for osteomyelitis and bone/joint infections (refer Appendices 8 & 9).

Comments:

Data indicate that a dose of 6 mg/kg/12 hrly for 3 doses followed by 6 mg/kg/day for 6 weeks (max 10 weeks) was effective in the treatment of osteomyelitis. Septic arthritis responded to double this dose.

5.2.4 Bacteraemia/Septicaemia: Data: One pivotal study; some data of non-pivotal nature in 2 studies (102-013 and 102-014) plus some information in two other studies (refer Appendices 8 and 9).

Pivotal study: Study 102-009: Randomised, double blind, comparative against vancomycin; 60 on teicoplanin evaluable. Dose 6 mg/kg/12 hrly 3 doses, then 6 mg/kg/day; Duration 10 days. Cure or improvement in 80% cases with both teicoplanin and vancomycin.
Non-pivotal data: Studies 102-13 and 014 showed 20/22 cured/improved with teicoplanin; however doses actually used in these patients cannot be clearly identified. Studies 102-001 & 002 and 86/12/1 (Appendices 8 & 9) cannot be assessed for this indication.

Comments:

Both teicoplanin and vancomycin were equally effective in bacteraemia/ septicaemia. No data on efficacy in vancomycin resistant infections or vancomycin intolerant patients.

5.2.5 Other infections:

No evaluable data provided on treatment of urinary tract infections, respiratory tract infections or treatment of peritonitis using peritoneal dialysis .

6. Product information:

-------- under negotiation --------

7. Delegate's conclusions and proposed action:

i) Quality of submitted clinical data and clinical evaluation report (despite discussions with evaluator) leave much to be desired. Quality of toxicology data were also less than satisfactory.

ii) No evaluable efficacy or safety data were provided concerning use in children. Kinetic data in children is contrary to physiological expectations.

iii) Dosage regimens used in various clinical trials appear to have been altered frequently during the course of the trial. No clear analysis of efficacy and safety was provided for the individual dosage regimens used in the various reported studies. Data analysis were not provided to establish that in Staph aureus endocarditis 20-25 µg/ml and in other infections was 10 µg/ml were the desirable plasma trough concentrations to aim for. Kinetic data to establish dosage regimens which would achieve these trough levels were also not provided. Optimum dosages remain unclear.

iv) Information concerning duration of treatment in the reported studies was confused and inadequate. The evaluator has recommended treatment durations as a guesstimate only.

v) No data were provided to define a population which could be treated appropriately by the IM route. After the distribution phase (following IVI) plasma time-concentration curves were identical for IV and IM routes.

vi) Proposed dosage regimen for patients with impaired renal function (normal dosage for 3 days then reduce) has not been justified with supporting evidence.

vii) No efficacy data have been provided for a number of proposed indications. Data, at best, support use in the treatment of Staph aureus infections of bones, joints and blood not responding to less toxic antibiotics (as is largely the case for vancomycin).

viii)The following options are put before the Committee for comments:

Option 1:

That the application for registration of teicoplanin be rejected in view of the many deficiencies in data as stated above.

Option 2:

That teicoplanin be approved as follows for the treatment of serious infections due to staphylococci or streptococci which cannot be treated satisfactorily with less toxic antibiotics, including beta lactam antibiotics:

Bone : osteomyelitis
Joints: septic arthritis
Blood: non-cardiac bacteraemia/septicaemia

Option 2 is favoured by the delegate as data appear to support the proposed limited use.

[redacted]

DIRECTOR, EU2
[EVAL]MAIN 4537

COMPUTER UPDATED

ENTERED WTA: JEB
VERIFIED WTA:
C/No: 91.156.2. Date: 27/10/93

8.

~~Appendix I~~

PRODUCT INFORMATION

TARGOCID (TEICOPLANIN for injection)

Description: Teicoplanin is a tetracyclic, glycopeptide antibiotic produced by Actinoplanes teichomycetes. It is presented as a sterile, pyrogen-free ivory white powder for reconstitution with water for injection. It is freely soluble in water and on reconstitution gives a clear solution.

~~Composition: Teicoplanin~~

~~Actions: Anti-microbial~~

Microbiology:

Teicoplanin ~~is generally~~ may be bactericidal or bacteriostatic on growing populations of susceptible Gram-positive organisms; ~~bactericidal synergism has been demonstrated with aminoglycosides.~~ depending on the sensitivity of the organism and antibiotic concentration. ~~One-step resistance to teicoplanin has not been obtained *in vitro*.~~

Some cross-resistance is observed between teicoplanin and the glycopeptide vancomycin. ~~among enterococci.~~

Teicoplanin has shown no cross-resistance to beta lactam antibiotics, macrolides, aminoglycosides, tetracycline, rifampicin or chloramphenicol.

Human **Pharmacokinetics:**

~~Following injection, teicoplanin rapidly penetrates into tissues, including skin, fat and bone~~ and reaches the highest concentrations in the kidney, trachea, lungs and adrenals. Teicoplanin does not readily penetrate into the cerebro-spinal fluid (CSF).

In man, the plasma level profile after intravenous administration indicates a biphasic distribution (with a rapid distribution phase having a half-life of about 0.3 hours, followed by a more prolonged distribution phase having a half-life of 3 hours), ~~followed by a slow elimination (with an~~ elimination half-life ~~of~~ is 70-100 hours~~)~~. The apparent volume of distribution at steady state is similar to total body water, i.e. 0.6 L/kg. ~~The volume of distribution in children is not substantially different from that in adults.~~

Approximately 90-95% teicoplanin is bound ~~with weak affinity~~ to plasma proteins. Teicoplanin penetrates ~~readily~~ into blister exudates ~~and into joint fluid; it penetrates neutrophils and enhances their bactericidal activity; it does not penetrate red blood cells.~~

~~When administered parenterally, the~~ Metabolic transformation is minor, about 3 %; about 80 % of administered drug is excreted in the urine over a 16 day collection period.

~~The elimination of teicoplanin from plasma is prolonged with a terminal half-life of elimination in man of 70-100 hours.~~

At the end of the distribution phase plasma levels, and the subsequent time-concentration curves, are identicle following intramuscular or intravenous administration of 3mg/kg dose (plasma levels of 7.1 µg/ml). Following intramuscular injection bioavailability is 100%; peak plasma levels are achieved in 3-4 hours.

and bone where it achieves peak levels comparable to those after intramuscular injection. Peak levels in joint fluid are approximately 60%. Teicoplanin penetrates poorly into subcutaneous fat and peritoneal fluid and almost not at all into CSF and red blood cells

Targocid is indicated for the treatment of the following serious infections due to staphylococci or streptococci, if such infections cannot be treated satisfactorily with less toxic agents, including beta lactam antibiotics:
Bone – osteomyelitis
Joints – septic arthritis
Blood – bacteraemia, septicaemia

Indications:

~~Targocid is indicated in the treatment of Gram-positive bacterial infections, even in those~~ patients with organisms resistant to standard therapy (including methicillin and cephalosporins) or who are allergic to penicillins and cephalosporins. Such infections include endocarditis, septicaemia and osteomyelitis, respiratory infections, skin and soft tissue infections, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis (CAPD).

Targocid is also recommended for prophylaxis in those patients in whom infection with Gram-positive organisms would constitute a hazard (for example in patients requiring cardiac, dental or orthopaedic surgery).

Contra-indications:

Targocid is contra-indicated in patients with known hypersensitivity to the drug.

Warnings and Precautions:

Periodic haematological studies, and renal and liver function tests are advised during prolonged treatment. Serial renal and auditory function tests should be undertaken in the following circumstances:

- Prolonged treatment in patients with renal insufficiency.
- Concurrent and sequential use of other drugs which may have neurotoxic properties. These include aminoglycosides, amphotericin, cyclosporin, cysplatin, frusemide and ethacrynic acid.

are no toxicity data on the concurrent use of these drugs with

However, there ~~is no evidence of synergistic toxicity with these combinations and~~ Targocid.

Targocid should be administered with caution in patients known to be hypersensitive to vancomycin since cross-sensitivity may occur. However, a history of the "Red Man Syndrome" that can occur with vancomycin is not a contra-indication with Targocid.

– The use of Targocid may lead to superinfection requiring appropriate treatment, including possible discontinuation of the further use of Targocid.
– Safety and efficacy of Targocid by the intra lateral route has not been studied

Interactions:

No data are available from properly monitored studies on interaction with other drugs.

~~In clinical trials Targocid has been administered to many patients already receiving various~~ medications including other antibiotics, antihypertensives, cardiac drugs, and antidiabetic agents, without evidence of adverse interaction.

Use in Pregnancy and Lactation: (Use in pregnancy category B3)

Reproductive studies in rats and rabbits with subcutaneous doses up to 200 mg/kg/day and 15 mg/kg/day respectively did not reveal teratogenic effects. Teicoplanin was associated with an increase in the number of stillborn pups when rats were treated with subcutaneous doses ≥ 100 mg/kg/day. Pup weight was reduced at all doses tested (SC doses ≥ 10 mg/kg/day). It is not known if teicoplanin is excreted in breast milk during lactation.

Targocid® should not be used during confirmed or presumed pregnancy or during lactation unless the benefits outweigh possible risks.

In clinical trials Targocid was associated with adverse reactions in 32% of the patients. However treatment was discontinued because of adverse reaction in 17% patients only. The most frequent adverse reactions were fever, rashes, nausea, vomiting, rigors, pruritus and diarrhoea.

Carcinogenesis and Mutagenesis

Long-term studies in animals to evaluate the carcinogenic potential of teicoplanin have not been performed. Teicoplanin was negative in assays evaluating the potential to cause gene mutations, but assays to evaluate the potential to cause chromosome damage have not been performed.

Adverse Reactions:

~~Targocid is generally well tolerated~~. The following adverse effects have been reported, ~~but a causal relationship has not been established in all cases:~~

- Local reactions: pain, phlebitis, redness, abscess rigor,
- Hypersensitivity: skin rash, erythema or pruritus, fever, bronchospasm or anaphylaxis increased
- Hepatic: ~~transient abnormality of~~ transaminases and/or alkaline phosphatase, hepatitis
- Haematologic: eosinophilia, thrombocytopenia, leucopenia
- Renal: ~~transient~~ rise in serum creatinine, blood urea, acute renal failure
- Gastrointestinal: nausea or vomiting, diarrhoea
- Nervous system: dizziness, headache
- Auditory: ~~tinnitus~~ hearing loss, tinnitus, ~~or vestibular disorder~~ vertigo

~~Targocid has been administered over a wide range of dosage in various clinical trials.~~ While the duration of therapy varied with the indication, the following table summarises the incidence (by dose) of key adverse events reported during these studies.

FREQUENCIES OF KEY ADVERSE EVENTS STRATIFIED BY DOSE

DOSE	<5 mg/kg (n=269)		5-10 mg/kg (n=598)		10-20 mg/kg (n=212)		>20 mg/kg (n=122)	
Adverse Event	n	%	n	%	n	%	n	%
Rashes	12	4.5	43	7.2	28	13.2	8	6.6
Fever	6	2.2	30	5.0	21	9.9	10	8.2
Pruritus	5	1.9	16	2.7	6	2.8	4	3.3
Rigors	0	0.0	17	2.8	8	3.8	6	4.9
Diarrhoea	7	2.6	20	3.3	7	3.3	4	3.3
Nausea &/or vomiting	8	3.0	30	5.0	19	9.0	7	5.7

Overdosage:

Treatment of overdosage should be symptomatic. Teicoplanin is not removed by haemodialysis or peritoneal dialysis.

Dosage and administration:

Note! Special instructions apply for reconstitution. See below

The reconstituted Targocid injection should be administered ~~directly either~~ intravenously ~~or intramuscularly. Intravenous dosing may be rapid over one minute, or more slowly~~ by infusion. ~~Dosage is usually once daily but a second dose may be given on the first day, for rapid attainment of high plasma levels.~~

over 30 minutes

~~An intramuscular injection of teicoplanin should not exceed 3 mL (400 mg) at a single site.~~ In the presence of shock or hypovolaemia I.M. administration should be avoided if intravenous administration is possible. Initial loading doses should be administered intravenously and intramuscular administration reserved for maintenance dosing after 3 or 4 days, depending on the clinical situation and response to therapy.

Adults:

~~In mild-moderate infections~~ (e.g. skin, soft tissue and urinary tract infections) treatment should be started with a single loading dose of 400-800 mg (or 6-12 mg/kg) by I.V. route; followed with 200-400 mg (or 3-6 mg/kg) daily by I.V. or I.M. route. Patients with a complicating illness such as cardiovascular disease or diabetes mellitus should receive a maintenance dose of 6 mg/kg/day.

~~In moderate infection (e.g.~~ septicaemia/bacteraemia, acute or chronic osteomyelitis) treatment should be started with 400-800 mg (or 6-12 mg/kg) by the I.V. route every 12 hours for 1 day; on subsequent days the dose should be 400 mg (or 6 mg/kg) daily.

~~Moderate-severe infection~~ (septic arthritis ~~and endocarditis~~)

Patients with septic arthritis should receive 800 mg (or 12 mg/kg) every 12 hours for 3 doses then a daily maintenance dose of 800 mg (or 12 mg/kg).

~~Patients with *Streptococcal* endocarditis should receive 400-800 mg (or 6-12 mg/kg) every 12 hours on day 1; on subsequent days a maintenance dose of 400-800 mg (or 6-12 mg/kg) should be administered daily.~~

~~Patients with *S.aureus* endocarditis should receive doses which maintain trough~~ serum concentrations above 20 µg/mL. This is generally achieved by administering 2 g (or 30 mg/kg) every 12 hours on day 1; on subsequent days a maintenance dose of 1 g (or 15 mg/kg) should be administered every 12 hours.

Elderly Patients:

As for adults. If renal function is severely impaired, the instructions for impaired renal function should be followed.

~~Children:~~

~~Adult doses on a mg/kg basis may be used as a guide; however, the rate of~~ clearance in children is uncertain and may exceed that in adults. Therefore, therapeutic monitoring of teicoplanin is desirable in children to ensure that trough

~~serum concentrations above 10 µg/mL are achieved (or 20 µg/mL in *S. aureus* endocarditis).~~

~~When serum concentrations of teicoplanin are monitored in moderate-severe infections, trough levels (immediately before the subsequent dose) should be above 10 µg/mL.~~

~~The majority of patients with infections caused by organisms sensitive to teicoplanin show a therapeutic response within 48-72 hours.~~ While the total duration of therapy is determined by the type and severity of infection and by the clinical response of the patient, the following periods are often appropriate:

- ~~Superficial infections - 1-2 weeks~~
- Uncomplicated bacteraemia - 2-4 weeks
- ~~Endocarditis,~~ septic arthritis and osteomyelitis - 3-6 weeks

Patients with Renal Impairment:

Please justify this statement on the basis of submitted data

For patients with impaired renal function, reduction of dosage is not required until the fourth day of Targocid® treatment. Measurement of the serum concentration of teicoplanin may optimise therapy (see "Dosage and administration").

From the fourth day of treatment

- **in mild renal insufficiency:**
  creatinine clearance between 40 and 60 mL/min, Targocid® dose should be halved, either by administering the initial unit dose every two days, or by administering half of this dose once a day.
- **in severe renal insufficiency:**
  creatinine clearance less than 40 mL/min, and in haemodialysed patients, Targocid® dose should be one third of the normal either by administering the initial unit dose every third day, or by administering one third of this dose once a day. **Teicoplanin is not removed by dialysis.**
- ~~in chronic ambulatory peritoneal dialysis:~~
  after a single loading I.V. loading dose, the recommended dosage is 20 mg/L per bag in the first week, 20 mg/L in alternate bags in the second week, and 20 mg/L in the overnight dwell bag only during the third week.

~~Prophylaxis:~~

~~Adults:~~

~~For Gram-positive cover during and after surgery (for example dental, orthopaedic or cardiovascular operations), an intravenous injection of 400mg Targocid should be given at the time of induction of anaesthesia. In cardiac surgery a further dose of 400mg should be given at the end of surgery, and another 400mg dose 24 hours later.~~

Note: The powder should be reconstituted strictly in accordance with the instructions below. Error may result in the formation of a stable foam and delivery of smaller doses.

DO NOT SHAKE

Preparation of Injection:

The entire contents of the water ampoule should be slowly added down the side wall of the vial of Targocid. ~~and~~ The vial rolled gently until the powder is completely dissolved, taking care to avoid foam formation. If the solution does become foamy, allow to stand for 15 minutes for the foam to subside. Satisfactory potency of the reconstituted injection is retained for 48 hours at 25°C ~~Room temperature~~ and for 7 days at 4°C.

Withdraw the entire contents into a syringe

The reconstituted solution contains - -- mg/ml of teicoplanin.

The reconstituted solution may be injected directly, or alternatively diluted with any of the following diluents:-

- 0.9% Sodium Chloride solution
- Compound sodium lactate solution

If necessary, ~~these~~ solutions with the above diluents may be stored at 4°C for up to 7 days. Solutions left at room temperature for longer than 24 hours should be discarded.

- 5% ~~Dextrose~~ glucose solution
- 0.18% Sodium Chloride and 4% ~~Dextrose~~ glucose solution

containing the above diluents (which contain glucose) should be stored at 4°C and

~~These~~ Solutions should be used within 24 hours; solutions kept longer than 24 hours should be discarded.

- ~~Peritoneal dialysis solutions containing 1.36% or 3.86% dextrose. Such solutions~~ are chemically stable for up to 28 days at 4°C. Teicoplanin is also stable in peritoneal solutions containing insulin or heparin at body temperature (37°C) for 48 hours.

Presentation

- Targocid 100 mg- 5 mL vial containing lyophilised 125 mg* teicoplanin and 14 mg sodium chloride with an accompanying ampoule Water for Injections (Ph. Eur.)
- Targocid 200 mg- 10 mL vial containing lyophilised 220mg* teicoplanin and 24 mg sodium chloride with an accompanying ampoule Water for Injections (Ph. Eur.)
- Targocid 400 mg- 20 mL vial containing lyophilised 460mg* teicoplanin and 24 mg sodium chloride with an accompanying ampoule Water for Injections (Ph. Eur.)

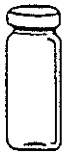
* An overage is included to allow withdrawal of the correct dose.

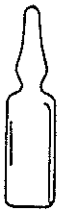
Manufactured/Supplied by:

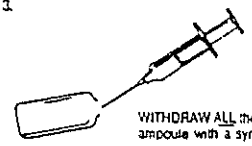
~~Further information available from~~ Marion Merrell Dow Australia Pty. Ltd.
Unit 1, 25 Frenchs Forest Rd. East
Frenchs Forest
NSW 2086

10/93

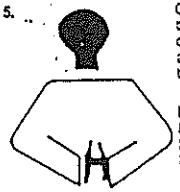
METHOD OF PREPARATION

1. 
Each vial contains TEICOPLANIN.

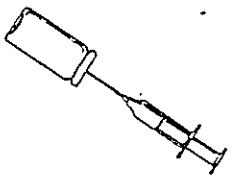
2. 
Each AMPOULE contains sterile Water for Injections.

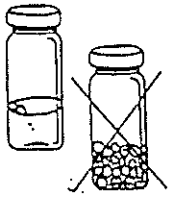
3. 
WITHDRAW ALL the water from the ampoule with a syringe.

4. 
SLOWLY inject all the water into the vial; about 0.2 ml of water will remain in the syringe.

5. 
GENTLY roll the vial between the hands until the powder is completely dissolved, paying attention to avoid the formation of foam.

IT IS IMPORTANT TO ENSURE THAT ALL THE POWDER IS DISSOLVED, EVEN THAT NEAR THE STOPPER.

6. 
Withdraw the teicoplanin solution slowly from the vial, trying to recover most of it by placing the needle in the central part of the rubber stopper.

7. 
The concentration of a carefully prepared solution will be 100 mg in 1.5 ml (from the 200 mg vial) and 400 mg in 3 ml (from the 400 mg vial). Shaking this solution will cause the formation of foam which will make it difficult to recover the expected volume. Nevertheless, if teicoplanin has been completely dissolved the foam does not change the concentration of the solution which will remain 100 mg in 1.5 ml (from the 200 mg vial) or 400 mg in 3 ml (from the 400 mg vial). If the solution does become foamy then it should be left to stand for about 15 minutes. It is important that the solution is correctly prepared and carefully withdrawn into the syringe; preparations that are not carefully executed can lead to the administration of less than 50% of the dose.