[redacted]

[redacted]

Paed[redacted]ian with a special interest in epilepsy in children and adults
Professor of Paediatrics, University of Sydney
Department of Paediatrics, Westmead Hospital, Westmead, Sydney, N.S.W. 2145. Australia

[redacted]

Drug Evaluation Branch,
TGA,
PO Box 100,
Woden.
ACT 2606.

RECEIVED
24 FEB 1993
DRUG EVALUATION BRANCH

23rd of February 1993.

Dear [redacted],

TEICOPLANIN EVALUATION.

Thank you for your letter of the 28th of January and for your comments on the draft copy of this evaluation.

It has been modified according to your suggestions and is enclosed in final form. Kindly acknowledge receipt.

Yours Sincerely,

[redacted]

[redacted]
Westmead Hospital,
Westmead,
Sydney 2145.
Australia.

Telephone [redacted]
FAX

MEMORANDUM OF FEES DUE TO

[redacted]

To:

The Director,
Drug Evaluation Branch,
TGA,
PO Box 100,
Woden 2606.

12th of January 1993.

Fee for the professional evaluation of 19165 pages of data and the provision of a report pertaining to:

TARGOCID - powder for injection, 100,200 and 400 mg.

LIASON OFFICER - [redacted]

SPONSOR - Marion Merrell Dow Ltd.

CONTROL NO: - 91. 2. 156. A.

TGA Reference 91/10911.

Sum, as agreed, in the TGA Standard Drug Evaluator Contract - 16.7.1992:

$ 17,833.00.

[redacted]

EVALUATION OF TARGOCID (Teicoplanin).

TABLE OF CONTENTS.

SECTION B - APPENDICES:

SECTION C.

SECTION A.

ASSESSMENT REPORT.

ASSESSMENT REPORT.

1.) TITLE: - EVALUATION OF A SUBMISSION FOR GENERAL MARKETING OF TEICOPLANIN (TARGOCID - Marion Merrell Dow.)

2.) FORMULATIONS: - lyophilised powder available as

* 100mg/5ml vials.
* 200 mg/10 ml vials.
* 400 mg/20 ml vials

for intravenous/intramuscular administration.

3.) THERAPEUTIC INDICATIONS: - Indications are for the treatment of Gram-positive bacterial infections including use in patients with infections resistant to standard therapy and those allergic to penicillins and cephalosporins. Such infections include: endocarditis, septicaemia, osteomyelitis, skin and soft tissues, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis. In addition, teicoplanin is indicated for the prophylaxis in surgical patients where infection with Gram-positive organisms are a potential hazard.

4.) STATUS IN OTHER COUNTRIES: -

a.) Approved:	Italy	-	April 1988.
	UK	-	February 1989.
	Denmark	-	February 1990.
	Holland	-	November 1990.
b.) Pending:	Sweden	-	Submitted May 1989.
	Canada	-	Submitted October 1989.
	USA	-	Submitted 1990.

5. PHARMACOLOGICAL EFFECTS AND MECHANISM OF ACTION.
Phillips G and Golledge C.L. (1)

Teicoplanin is a glycopeptide antibiotic with bactericidal activity against most Gram-positive organisms including multiresistant cocci. It is in the same class of antibiotic as vancomycin.

Glycopeptides are large molecules which inhibit a late stage of peptidoglycan synthesis in the cell wall of most Gram-positive bacteria. They affect dividing organisms only and are not effective against Gram-negative organisms. As the site of action differs from that of the Beta lactam antibiotics, there is no cross resistance.

Teicoplanin can be given i.m., as well as i.v. and is usually administered once daily due a prolonged half life. Minimal and maximal doses relate to the MIC of the organism(s) being treated and thus will vary from patient to patient. Measurement of serum levels may on occasion be of some value, but are not essential to management. However, in general, predose levels should be > 10 mg/l with 1 hour post dose concentrations of 25 - 50 mg/l. Side effects appear to be less, and less sever, than for vancomycin and include: allergy, skin reactions, bronchospasm, pain at the i.m. injection site. Ototoxicity and nephrotoxicity are uncommon.

6. PHARMACOKINETICS.

This data is summarised in the text, with major, pertinent studies tabulated in Appendix 1. Lesser studies are briefly discussed in the text at the end of this section. [References labelled (--) refer to the sponsor's references for individual studies as shown in B3, Volume 1, pages 55 - 59.

These studies used 4 assay methods - microbiological (especially, detection limit = 0.05 mg/l), HPLC, radiolabelled and an enzyme receptor assay. Data from 28 studies are submitted including observations in the elderly, children, renal failure and situations where tissue penetration could be studied. The drug is unusual with a very long half life allowing once daily dosing.

Absorption: - teicoplanin is not orally absorbed, but exhibits 94% bioavailability after i.m. administration of 3mg/kg in healthy volunteers with Cmax of 7.1 +/- 1.8 mg/l and Tmax 2.0 +/- 1.1 hours (Ref 2). This was maintained with repeat i.m. dosing with Day 5 trough levels of 5.4 - 7.3 mg/l (Ref 6). There was no data on i.m. dosing at 6mg/kg, but in view of the data at 3mg/kg it could be assumed that this would be adequate.

Distribution: - following single i.v. doses of teicoplanin, plasma concentration - time profiles indicate a prolonged biphasic distribution phase best described by a 3 compartment open model with t 1/2 α ranging from 0.17 - 0.51 hours to t 1/2 β 1.62 to 4.1 hours and a volume of distribution of 0.7 - 0.8 1/kg (Refs 1,2,4,14) i.e into total body water.
Single i.v. dose healthy volunteer studies from 3 to 6 mg/kg showed C max values from 53.5 +/- 22.2 to 111.8

+/- 43.4 mg/l with 24 hours post dose levels of 2.1 to 4.2 mg/l; above the MIC of most of the teicoplanin sensitive organisms. Teicoplanin is some 90% protein bound (Ref 19) with little penetration into RBC (14) , CSF (19), but clinically potentially useful penetration into bone (20), synovial fluid (21), lung tissue (22), pleural fluid (23), fat (24), blister fluid (15) and peritoneal fluid (15). (For details see pages 6 and 7.)

Metabolism: - teicoplanin is excreted almost totally unchanged in the urine and no metabolites have been identified (Ref 4,14). Eighty percent of a single dose of 400 mg is recovered from urine by 384 hours.

Elimination/Excretion : - elimination is slow with a half life ranging from 70 to 100 hours with total body clearance (Cl t) and renal clearance (Cl r) 15.7 =/- 1.3 ml/h/kg and 9.3 +/- 0.8 ml/h/kgg respectively. Rate of elimination was not affected by dose, route of administration or cumulative dosing - Ref 25, Appendix 1. [Because of the importance of renal excretion of this drug, Clr has been allocated a specific column in Appendix 1.]

PHARMACOKINETICS IN PATIENTS (as opposed to healthy volunteers).

a.) Patients with renal impairement:
Excretion of teicoplanin is decreased (Table 1.) with progressively deteriorating renal function (Ref 26). Further data (Ref 28,29,30)(Appendix 1/3) has confirmed these observations and have demonstrated that teicoplanin is barely cleared by haemo or peritoneal dialysis. Drug accumulation in renal failure has not been associated with clinical toxicity and thus it is proposed by the investigator that normal dosing should be given for several days and then patients should receive 200 mg every 2 to 3 days. (Ref 26 - Appendix 1/2) [Other dosage recommendations are shown on Page 8).

	T 1/2 hours	CLr ml/h/kg	AUC 0 -120 h mg.h/l
6 normal volunteers Creat.Cl 107 ml/min	62 +/- 5	9.3 +/- 0.8	197 +/- 15
6 patients: moderate renal failure - Creat.Cl 57 ml/min	96 +/- 19	3.2 +/- 1.5	326 +/- 42
5 patients: severe renal failure - Creat.Cl 11.8 ml/min	111 +/- 15	0.6 +/- 0.1	409 +/- 72

TABLE 1. showing data from 6 healthy volunteers and 11 patients with renal failure after receiving a single dose of 3 mg/kg intravenously of teicoplanin.

b.) Kinetics in the elderly:

Data collected over 7 days from 12 patients (ref 32) with mean creatinine clearances of 51.3 +/- 4.1 ml/h/kg given a single i.v. dose of 6 mg/kg of teicoplanin showed T 1/2 of 114.3 +/- 8.6 hours , CLr 3.84 +/- 0.36 ml/h/kg and Vd 1.70 +/- 0.19 l/kg. These data reflect the renal impairement associated with ageing and an enhanced volume of distribution (Vd) , probably reflecting the lipid solubility of teicoplanin and enhanced body fat in this group of subjects. The observed pharmacokinetic changes , compared to younger adults, were small and thus advancing age per se, should not alter teicoplanin dosage requirements.

c.) Kinetics in children:

In 2 studies (Ref 33, 34), 20 children aged 2 to 13 years were studied; these were mainly patients who received the drug prophylactically. Half life was unexpectedly shorter in children and especially neonates particularly in Ref 34 (Appendix 1/4) This needs to be explored further - see page 39.

d.) Miscellaneous factors:

From the evaluable data there was no suggestion that ethnicity, sex or other other intercurrent disorders affect teicoplanin metabolism to a clinically significant degree.

COMMENTS ON LESSER STUDIES or those which cannot be suitably tabulated:

Ref 3- B3- 2/257: this study contributes little , being a very early study using low doses (1 - 85 mg). It did however show that in volunteers, no drug was orally absorbed in doses from 50 - 750 mg.

Ref 13 - B3 - 2/355 : oral administration to 2 groups of 6 volunteers , 250 and 500 mg respectively, showed no absorption.

Ref 15 - B3 - 3/457: this study of 12 children (8 girls) aged 1 - 15 years , weighing 8 - 58 kg, was a dose finding study. Three, 4 or 5 mg/kg were given i.m. or i.v. with sampling to 120 hours and assayed by an enzyme receptor technique. The data as presented is incomplete with scant blood level information thus making the dosage recommendations difficult to follow. It is proposed that a dose of 3 mg/kg produced unsatisfactory peak and trough levels and that 6 mg/kg should be administered initially followed by 3 mg/kg, which gives good peak, but poor trough, levels.

Refs 17/18 - B3 - 3/467 and 3/485: two protein binding studies. In Ref 17, 14 C labelled teicoplanin was studied in vitro by equilibrium dialysis using human serum albumin. In Ref 18, samples were colected from volunteers who had received 14 C teicoplanin i.v. and again were studied by equilibrium dialysis. Both studies showed that about 90% of the teicoplanin complex is plasma protein (albumin) bound.

Ref 19 - B3 - 3/489: a French study investigating CSF penetration in 7 adult patients with meningitis receiving amoxycillin. On Days 2 & 5, patients were given 400 mg tecoplanin i.v. and CSF was obtained in various of the patients 2 to 8 hours after the dose. In only one patient were CSF levels of 0.8 mg/l (Day 2) and 1.1 mg/l (Day 5) detected. In all other patients, CSF levels were < 0.3 mg/l. It was thus concluded that in the dose employed that teicoplanin barely penetrates the CSF.

Ref 20 - B3 - 3/505: Microbiological assay study carried out in France in 30 patients undergoing total hip replacement who were divided into 5 groups each receiving 6 mg/kg i.v. at different times before surgery (times are shown below). (Standard deviations in brackets.)

Time h.	Serum mg/l.	Spongy bone ug/g.	Compact bone ug/g.
0.5	46.3 (11.0)	10.8 (6.8)	6.1 (1.7)
4	8.5 (2.1)	6.3 (3.1)	4.6 (1.2)
8	6.5 (0.8)	6.6 (2.9)	4.9 (0.5)
12	4.1 (0.8)	6.3 (3.0)	4.9 (21.)
24	3.3 (1.7)	7.1 (5.4)	4.0 (2.5)

It was concluded that teicoplanin penetrates bone well. Technically there would have been little chance of contamination with residual blood

Ref 21- B3 - 3/513: Microbiological assay study of 22 patients with an acute exacerbation of a chronic joint problem, given 400 mg i.v. as a single dose and divided into 4 groups to collect serum and SYNOVIAL FLUID at 6,12,24 or 48 hours. Mean synovial fluid concentrations at 6 hours were 4.0 +/- 1.4 mg/l and 1.4 +/- 0.4 mg/l at 24 hours; the latter being lower that the MIC for Staph. Aureus. To treat septic arthritis either a higher dose or initial greater dosage frequency is needed.

Ref 22 - B3 - 3/521: penetration into LUNG TISSUE was studies using a microbiological assay in 14 patients (200 mg i.v. single dose) and 12 patients (400 mg i.v.) undergoing lung resection for carcinoma. Serum and tissue concentrations measured at 30 and 60 minutes after dosing:

		200mg i.v.	400 mg i.v.
30 minutes:	serum	20.9 mg/l	38.2 mg/l
	lung tissue	4.7 mg/l	9.5 mg/l
60 minutes:	serum	13.2 mg/l	18.0 mg/l
	lung tissue	3.8 mg/l	4.9 mg/l

A correction was made for the amount of antibiotic in the blood within the lung (B3 - page 525).

Ref 23 - B3 - 3/531: an investigation of PLEURAL FLUID penetration in 5 patients using an unspecified immunological assay after a single 400 mg i.v. dose. Due to the brevity of the data, it can only be said that mean peak pleural fluid levels at 5 hours post dose were 2.8 +/- 0.5 mg/l and 7.5 +/- 1.5 mg/l in patients who had 2 doses of 400 mg i.v. 12 hours apart.

Ref 24 - B3 - 3/533: penetration into SUBCUTANEOUS FAT was studied in Leeds in 28 patients undergoing arterial reconstruction with serum and groin fat samples obtained after a single 400 mg i.v. dose; 1,3,6 or 12 hours pre-operatively. Levels fell from a mean of 1.03 mg/l at 1 hour to 0.6 mg/l at 12 hours. Teicoplanin penetrates adipose tissue, but in the dose given did not exceed the MIC for Staph. Aureus. Contaiminating blood was removed from the tissue samples by physical wiping.

Ref 25 - B3 - 3/539: represents accumulated random serum teicoplanin concentrations from 204 patients from 21 centres. It was not felt that this data contributed greatly to the evaluation as there is an absence of kinetic, clinical, bacteriological or efficacy information.

Ref 27 - B3 - 4/599: 15 ICU patients with a variety of severe illnesses and variable renal function were given a single dose of 400 mg i.v. This data does not add to the evaluation as samples were only collected for 48 hours i.e. about half of teicoplanin's half life.

Ref 30 - B3 - 4/721: a study conducted in the UK in patients on CAPD or haemodialysis. The pharmacokinetic data is similar to that of Refs 29 & 29 (Appendix 1), but this study offers 2 practical suggestions, supported by evidence of clinical efficacy:
* For treating Gram positive peritonitis, recommended an i.v. dose of 200 mg followed by intraperitoneal administration of teicoplanin using 40 mg per 2 litre exchange.
* For haemodialysis patients with Gram positive infections recommended a dose of 200 mg i.v. every 48 hours.

Ref 31 - B3 - 4/737: A study from Manchester in CAPD PERITONITIS initially using 50 mg per 2L bag for 48 hours and 25 mg/bag thereafter. Dialysate fluid concentrations ranged from 14 - 18 mg/l with corresponding serum concentrations of 2.5 - 5.5 mg/l. Peritoneal fluid became sterile within 24 hours.

DOSAGE RECOMMENDATIONS IN RENAL FAILURE:

Ref 28 - B3 - 4/696 - APPENDIX 1/3: refers to a 400 mg i.v. dose

	DEGREE OF RENAL INSUFFICIENCY-creatinine Cl		
	> 80 ml/min	30-80 ml/min	< 10 ml/min
Constant dosage interval, variable dose:			
Dose (Fraction of normal)	1	1/2	1/3
Dosage interval (multiple of normal)	1	1	1
Variable dosage interval, constant dose:			
Dose (Fraction of normal.)	1	1	1
Dosage interval (Multiple of normal.)	1	2	3

Ref 29 - B3 - 4/703 - APPENDIX 1/3: in patients on CAPD , it suggested that a loading dose of 3 mg/kg should be followed by the same dose every 3rd day or 1/3rd of the dose (100 mg) daily.

These recommendations are based on pharmacokinetic evaluation and extrapolation and were not tested for clinical efficacy.

GENERAL PHARMACOLOGY OBSERVATIONS.

6/951 - 963: 8 male volunteers (29 - 47 years) received 400 mg teicoplanin i.v. or saline (double blind). No change in bronchomotor tone, blood pressure, heart rate and routine haematology/biochemistry (detailed data not shown) was observed. This was a good study.

6/ 965 - 971: blood pressure and heart rate were assessed for 10 minutes before and after rapid i.v. boluses of 200 or 400 mg in patients with Gram positive infections. No significant changes were observed in systolic BP (n = 219), diastolic BP (n = 218) or heart rate (n = 203). A sound study.

6/ 973 - 989: In vitro study in concentrations ranging from 10 - 5,000 mcg/ml, no change was observed in platelet aggregation, release of 5 HT from platelet rich plasma or agglutination of fixed washed platelets in the presence of excess factor VIII. Ristocetin and vancomycin were used as controls, with the former showing some effect at > 600 mcg/ml and the latter at 5000 mcg/ml.

6/ 991 - 1003: similar to the preceding study with the same results.

6/ 1005 - 1018: a similar in vitro study to the preceding two. In high concentrations, 5 and 10 mg/ml (well above therapeutic concentrations) higher spontaneous platelet aggregation was observed as was inhibition of platelet aggregation by ADP, collagen and ristocetin.

Six volunteers and 6 patients received 400 mg i.v stat and 200 mg i.v. for 7 days. No changes were observed in platelet count, bleeding time, plasma B-thromboglobulin, APTT, PT, thrombin clotting time or FDPs at 0, 3 and 7 days of treatment and 3 days later. A good study.

6/ 1019 - 1090: teicoplanin concentrations from 70 mg/l (therapeutic) to 700 mg/l were studied for RBC haemolysis in vitro. No haemolytic potential was observed at any concentration. A methodical study.

CLINICAL TRIALS.

Data from 9 trials, 6 considered pivotal, were submitted by the sponsor. These will be discussed in the text with a summary Appendix for each study.

PROTOCOL 102 - 013. VOLUME 7 p 1196. APPENDIX 2.

TITLE: An open study of teicoplanin in the treatment of intravenous drug abuse associated endocarditis caused by Gram-positive bacteria.

The study was designed to assess the efficacy and safety of teicoplanin in patients with bacteraemia due to susceptible gram - positive bacteria whilst also investigating the susceptibility of various pathogens to teicoplanin, vancomycin and penicillinase resistant penicillins (this secondary objective is less cogent to the present evaluation.)

Patient data , dosage, duration of therapy is noted in Appendix 2.

With regard to EFFICACY:- 40 patients were deemed evaluable. Those deemed unevaluable were thus classified with 25 inappropriate or with no isolated pathogen, 5 treated , 5 days due to an ADR, 4 treated for < 5 days for other reasons, 2 Gp A Beta Haemolytic Strep, 2 interfering antimicrobials, 2 inadequate pretreatment cultures, 1 bacteriological diagnosis unclear and 1 assessment of response unclear. Thirty one had endocarditis (24 Staph Aureus and 7 streptococci) and 9 had non cardiac bacteraemia (4 Staph Aureus and 5 streptococci). In the 9 non cardiac bacteraemia, all were cured or improved with a mean dose of 19 mg/kg/day (range 7 - 29 mg/kg/day.) As will be observed in the dosage section of Appendix 2, the dose was increased on 4 occasions during the course of the study, as the initial doses were found to be ineffective. Twenty three of the 31 patients with endocarditis were treated with doses > 20 mg/kg/day with the remaining 8 patients receiving doses from 6.5 - 17.7 mg/kg/day. Seven of the patients with endocarditis were infecetd with streptococci ; 5 were cured/improved, 1 failed therapy and 1 relapsed. Of the 24 patients with Staph Aureus endocarditis, 15/24 were cured/improved with a mean dose of 24 mg/kg/day. It would seem that there is a need to achieve serum teicoplanin levels of > 20 mg/l for the first week of therapy for success in Staph Aureus endocarditis (10/11 cases).

The doses used were much higher than those recommended in the PI (see page 23).The safety analysis does not separate the higher and lower dosage groups.

BACTERIOLOGICAL EFFICACY was as follows:

	Organism.	Elimination.
Non Cardiac Bacteraemia.	Staph Aureus MR*	1/1
	Staph Aureus MS*	3/3
	Strep. B. Haemolytic	0/1
	" Gp. A.	2/2
	" Gp. G.	3/3
Endocarditis patients.	Staph Aureus MR*	3/6
	Staph Aureus MS*	12/18
	Strep. Anginonus	1/1
	" Gp. A.	1/1
	" mitis	1/2
	" salivarius	1/1
	Viridans Strep.	3/3
	Corynebacterium	1/1
	Peptostreptococcus Magnus	1/1
	" Micros	1/1

* MR = Methicillin resistant. MS = Methicillin sensitive.

Looking at SAFETY, bearing in mind that the patients studied were i.v drug abusers, the following was observed:

Clinically significant increases in SGOT were seen in 18/61 patients, 14/57 SGPT, 13/62 alkaline phosphatase, 5/61 for total bilirubin, 3/60 creatinine, platelet decrease 3/61 and neutropenia 6/53.

One patient showed a deterioration in audiometry but there was no clinical change in hearing. It is uncertain how many of these laboratory changes are drug related or are related to the underlying disorder where many such changes might be expected. Table 9 (7/1222) supports this contention with 23/40 patients showing significant complications of their disorder. In addition, 95% of the patients were receiving other medications, with one patient receiving 29 medications. The data just presented differs from the data in the sponsors summary, probably for these reasons. Clinical adverse events are shown in Appendix 2.

There were 51 ADRs amongst the 27 patients in whom these occurred, with 12 described as severe - these were a mixture of fever, rash, chills, abnormal hepatic function, thrombocytopenia and a seizure). In the latter group, teicoplanin was ceased in 6 patients; 4 recovered from the ADR and in 2 cases this was uncertain. In the remaining 6 patients in whom the drug was continued, ADR recovery was seen.

Three patients died during the study : 2 due to myocardial infarction and one from an intracerebral bleed.

PROTOCOL 102 - 014. VOLUME 14 p 2471.- APPENDIX 3.

TITLE: A randomised blinded comparative study of teicoplanin versus vancomycin in the treatment of non vascular access associated bacteraemia/endocarditis caused by Gram - positive bacteria.

This study sought to evaluate the efficacy and safety of teicoplanin in patients with bacteraemia due to Gram-positive organisms and to compare this to the efficacy of vancomycin. Patient data, dosage, duration of therapy are noted in Appendix 3.

Randomisation led to 50 patients receiving teicoplanin (T) and 56 vancomycin (V); of these 27 and 25 were deemed evaluable respectively for efficacy; all could be assessed for safety. The reasons for the not being evaluable were: inappropriate patient or no pathogen 8 T and 14 V, , 5 days treatment 8 T, 10 V, interfering antimicrobial 3 each, clinical response unclear 1 T, 2 V, Gp A Beta Haem Strep 1 T, inappropriate primary infection 1 T, resistant pathogen 1 T, bacteriological diagnosis unclear 1 V and 1 V inadequate pre-treatment culture.

In terms of EFFICACY: in the noncardiac bacteraemia patients with teicoplanin 11/13 (84%) were cured/improved as opposed to 13/19 (68%) with vancomycin; i.e equally effective. Ten of the 13 T patients were infected with Staph Aureus and 9/11 V patients. Looking at the endocarditis patients, 3/14 T patients (21%) were cured/improved and 5/6 for vancomycin (83%). Twelve of the 14 T patients were infected with Staph Aureus and 4/6 V cases. In patients with noncardiac bacteraemia, response was independent of trough T concentrations. In those with endocarditis the mean trough T concentration was 11.0 mg/l (4.8 - 19.8) and vancomycin 11.0 mg/l (1.6 - 27.5). These data suggest that teicoplanin is not very effective in Staph Aureus endocarditis at the serum levels achieved in this study. Again, the need for an increased should be reflected in the PI.

SAFETY: this is slightly difficult to assess with respect to laboratory criteria due the nature of the underlying disease and because many patients had abnormal baseline results. Taking this into account, the investigators concluded that firstly the number of ADRs that could be directly drug attributed was quite small (Appendix 3) and that there was no significant difference between T and V. One vancomycin patient showed a deterioration in audiometry and another had tinnitus. One T and 3 V patients discontinued treatment due to ADRs.
Ten patients in the teicoplanin and 7 vancomycin patients died during the study. Review of the data does not suggest this to be drug related, but reflecting the severe nature of their disease.

PROTOCOL 102 - 007. VOLUME 23. PAGE 3935. APPENDIX 4.

TITLE: A randomised open study of teicoplanin versus cefazolin in the treatment of moderate to severe skin and soft tissue infections caused by Gram - positive bacteria.

The primary objective of this study was to evaluate the efficacy of teicoplanin i.m. and i.v. at 3mg/kg/day (later amended to 6 mg/kg/day) compared with cefazolin in standard dosage. Basic data from this study is summarised in Appendix 4.

This was an open, randomised, Phase III study of 680 patients: - 418 in the randomised and 262 in the non-randomised arms. Of the 418 patients in the randomised arm, 82 teicoplanin i.m., 106 teicoplanin i.v. and 105 cefazolin were evaluable for efficacy. The majority of those who were not evaluable did not have a pathogen isolated (n = 60), 24 patients were treated < 3 days, in 13 cases there was no susceptibility testing, in 6 patients the organism was not Gram-positive, in 5 cases the infection was inadequately documented and there were a miscellnany of reasons in the remaining 17 patients. There were 262 patients in the non-randomised group with 181 being evaluable for efficacy. The commonest reason for not being evaluable was an inappropriate or no pathogen (n = 30), 10 cases were treated < 3 days, in 9 cases the organism was not Gram positive and there were a miscellany of reasons in the remaining patients.

In randomised patients, the pre-amendment average daily doses were 3.4 mg/kg i.m. and 3.59 mg/kg i.v. teicoplanin and 37.9 mg/kg cefazolin. Post-protocol amendment, the average doses were 6.62 mg/kg i.m., 6.87 mg/kg i.v. and 35.9 mg/kg cefazolin. In the non randomised groups, the pre-amendement dose was on average 5.5 mg/kg increasing after the amendment to 6.6mg/kg. Clinical and bacteriological EFFICACY was as follows in the randomised study:

Randomised Group -	CURE OR IMPROVEMENT.		
	T i.m.	T i.v.	Cefazolin
Teicoplanin (T) 3 mg/kg/day dose	44/50 (88%)	54/60 (90%)	63/66 (95%)
Bacterial elimination	<---- 85/98 (87%) ----->		55/63 (87%)
Teicoplanin (T) 6mg/kg/day dose	30/32 (94%)	46/46 (100%)	38/39 (97%)
Bacterial elimination	<-----73/76 (96%)------>		30/38 (79%)

In the non-randomised patients, in the lower dose group, clinical cure/improvement was seen in 138/151 (91%) and in the higher dose group 30/30; suggesting the lower dose to be effective.

The commonest pathogens were Staph.Aureus, Staph.Epidermidis, coagulase negative Staph and Gp.A Streptococci. Elimination rates for these organisms ranged from 88 - 100% for teicoplanin and 82 - 93% for cefazolin and reflect PI dosage recommendations.

Adverse reactions in the randomised patients were infrequent with those probably attributable to teicoplanin shown in Appendix 4. Discontinuation of the administered drug occurred in 6/148 T i.v., 8/125 T.i.m. and 6/140 cefazolin patients: this was usually associated with rash or fever i.e. hypersensitivity reactions. Local reactions with i.m. administration of either T or cefazolin were most uncommon. Two patients receiving T died; neither could be shown to be drug related. Ninety percent of the patients were taking concomitant medications most commonly aztreonam or metronidazole to provide Gram-negative/anaerobic cover in the teicoplanin cases; these were the only additional antibiotics permitted.

In the non-randomised group, 25/281 patients discontinued due to ADRs, again usually rash/fever. In 20/25 patients it was felt by the investigators that teicoplanin was causative, whilst the sponsors felt that this was 15/25. Three patients in the non-randomised group died; all due to underlying disease processes. It should be mentioned that about 40% of the patients had cardiovascular disease and about 25% had diabetes mellitus. (pages 4323 - 4326 and 4457 - 4458)

This data concluded that teicoplanin and cefazolin were comparable in treating moderate to severe skin and soft tissue infections with clinical success seen in > 90% of patients. With complicating illnesses such as diabetes mellitus or significant cardiovascular disease, teicoplanin 6 mg/kg/day was comparable to cefazolin.This dose is higher than that recommended in the PI and should be added thereto. The ADR profile was similar with both drugs.

PROTOCOL 102/009. VOLUME 52. PAGE 9601.-APPENDIX 5.

TITLE: A randomised, blinded, comparative study of teicoplanin (T) versus vancomycin (V) in the treatment of vascular access associated bacteraemia/septicaemia caused by Gram-positive bacteria.

This study is summarised in Appendix 5. Its purpose was to evaluate the efficacy and safety of teicoplanin compared to vancomycin in this particular clinical setting. To cover possible Gram-negative infections, the use of numerous appropriate antibiotics was allowed for the first 72 hours in addition to the study drugs and were ceased if Gram-negative cultures were not obtained. This could of course have had some impact on the observed efficacy of the study drug, although it may have had the same effect for both T and V. It does however complicate the evaluation of these results.Serum teicoplanin levels were measured by microbiological assay with Bacillus subtilis ATCC 6633 as the test organism. Serum vancomycin and gentamycin levels were also measured. As in previous studies, quite numerous patients could not be evaluated for efficacy: 58 for both T and V with the majority being due to inappropriate or absent pathogens or because treatment was for less than 5 days.

Clinical and bacteriological EFFICACY data is shown in Appendix 5 with similar results for T and V. Again T dose at 6 mg/kg was higher than that recommended in the PI for maintenance therapy.pp At follow up (1 to 4 weeks), 37 of the T and 38 osgsg16f the V were still cured or improved; 5 T and 6 V patients had relapsed. The mean serum trough teicoplanin concentrations in the patients assessed for efficacy was 10 ug/ml although there were 4 patients who due to an antimicrobial interacting with the assay, had levels > 50 ug/ml. Vancomycin trough levels were on average 13 ug/ml. There was no apparent relationship between trough levels and clinical outcome.In fact, half of T cures had trough levels < 10ug/ml.

The commonest pathogen was Staph Aureus; eliminated in 24/31 (77%) T and 23/29 (79%) V. The second commonest organism was Staph epiderdimis; eliminated in 17/20 (85%) T and 20/22 (91%) V. Most of the latter were methicillin resistant : 13/20 and 12/22. Clinical failures in evaluable patients were similar in both groups and were most often associated with Staph Aureus. In a proportion of these patients, the infected catheters were not removed (T = 10 and V = 14), thus allowing a physical perpetuation of the infected source.

As in previously discussed studies, as the patients were septicaemic and quite ill (largely cardiovascular disease, diabetes and renal disease), pretreatment laboratory tests were quite frequently abnormal.Taking this into account, ADRs were reported in 32/117 T and 37/121 V patients with 7 and 8 discontinuations respectively. The nature and extent of the ADRs were similar in both groups. Audiometry showed a deterioration in hearing in 4 T and 5 V patients and an improvement in hearing in 3 patients in each group. There were 18 deaths in the T and 23 the V group; all of which were attributable to their underlying problems.

The study concluded that T and V were equally effective in treating vascular access associated bacteraemia due to Gram-positive organisms with sidse effects being similar with the 2 drugs.

PROTOCOL 102 - 012. VOLUME 64. PAGE 12154. APPENDIX 6.

TITLE: An open study of teicoplanin in the treatment of acute bone and joint infections caused by Gram-positive bacteria.

The primary objective of this study was to evaluate the efficacy and dafety of teicoplanin i.v. or i.m. in hospital or on a subsequent outpatient basis to patients with Gram positive bone and joint infections. Basic data is summarised in Appendix 6. As there shown, there was an amendment to the dosage schedule during the study when it was apparent that the initial dose (6 mg/kg/day) was not proving to be effective in patients with septic arthritis. On increase to 12 mg/kg/day, success rate rose from 64 to 94%. In osteomyelitis, success rates were similar in 6 and 12mg/kg/day groups.

62% of the 207 patients classified as cured/improved at the end of the treatment period were followed up (osteo > 150 days post treatment and septic arthritis > 28 days post treatment)with a total of 14 relapses. This relapse rate is probably comparable to that seen with other antibiotics in the same clinical setting.These occurred in osteomyelitis mainly within 50 days of the cessation of treatment and in septic arthritis at 1 week, 44,130 and 211 days.

Bacteriologically, the results were:

ORGANISM	Number eliminated/ number of patients.
Staph. Aureus.	110/135
Staph. epiderdimis.	33/36
Staph Aureus (MR)	17/21
Other Staph.	29/41
Streptococci	23/29
Enterococci.	18/19
Miscellaneous	11/14.

Of the 342 patients entered, 166 reported adverse events, 119 felt to be teicoplanin related, with 59 patients discontinuing as a result. These patients were less ill than the previously described iv drug users and thus this ADR rate seems high and will thus be presented in a bit more detail than in the other studies. There were 7 deaths during the study, but these could not be shown to be drug related. ADR data can be looked at in 2 groups of patients; those who continued with T after reporting an ADR = 166 - 59 - 7 = 110 patients and then in the 59 patients who discontinued treatment.

ADR.	Number of patients (n = 110*/342.)
Hypersensitivity (n = 88)	
Chills	18
Eosinophilia	7
Erythema	5
Erythema Multiforme	2
Fever	38
Flushing	5
Macular rash	1
Papular rash	2
Pruritic rash	5
Pruritis	14
Rash	35
Hepatotoxicity (n=10)	
Hepatotoxicicty	1
Significantly altered enzymes	9
Nephrotoxicity (n=4)	
Urea/creatinine increased	3
Acute renal failure	1
Ototoxicity (n=18)	
Dizziness	11
Hearing impaired	2
Tinnitus	4
Vertigo	2
Haematological (n=9)	
Leukopenia	3
Neutropenia	3
Thrombocytopenia	4

* A patient may have reported more than 1 adverse event per category.

With respect to the 59/342 patients who discontinued due to ADRs, the majority were related to fever and/or rash and in 53 cases, the investigators felt that the ADR was teicoplanin related with the sponsor feeling that in a further 14 cases the ADR may have been related to another drug or the disease process. Of the 59 patients, 50 recovered, 7 were still under treatment and in 2 cases, there was no data. As in previous studies, 330/342 patients were taking other medications. As in previous studies there was a high incidence of concomitant diseases, especially cardiovascular, diabetes, musculoskeletal and recent surgery (p 12443.)

During treatment 25 patients developed superinfections. It is difficult to ascertain if these were drug related with teicoplanin being discontinued in 3 instances (p 12710). There were 13 treatment failures (p 12724) which were largely associated with destructive lesions/abscesses needing surgical management.

This study concluded that teicoplanin is effective in the treatment of acute and chronic osteomyelitis at a dosage of 6 mg/kg/day i.v. or i.m. as well as in septic arthritis with a dose of 12mg/kg/day. It also concluded that the ADR rate, especially of hypersensitivity reactions, is higher than previously discussed studies. Whilst it is suggested that this could be dose related, the evidence for this is scant. From the data presented, there is no obvious reason as to why this should be.

PROTOCOL 102 -019. VOLUME 85. PAGE 16228. APPENDIX 7.

TITLE : A multicentre randomised, blinded, comparative study of teicoplanin dosing regimens and vancomycin in the treatment of endocarditis and bacteraemia of non-cardiac origin caused by Gram - positive bacteria.

This study, whilst major in intent, had a cut off period for enrolment and because of the high drop out and unevaluable rates in this particular population, there were eventually only 62/132 patients suitable for efficacy assessment. Once these were subdivided into groups (Appendix 7 - Results column), the numbers became quite small and it was difficult to draw efficacy conclusions. As a result this study will be presented in summary form (Appendix 7.)

As with other studies, a number of antibiotics were used for the first 48 hours to cover possible Gram-negative infections. The main reasons for the high number of unevaluable patients (66/132) were an absence of pathogens or treatment < 7 days. Only 40 patients (21 T and 19 V) completed treatment i.e. 92 patients (T 50, V 42) discontinued the study. Again the " No pathogen isolated " group was the largest (n = 49), 9 died, 8 were dropped due to " inneffective treatment " and 5 discontinued due to ADRs. As with other studies, many patients had other problems with 60 - 70 % being drug abusers and 25 - 30% alcohol abusers.

The results of treatment are shown in Appendix 7 and whilst there was follow up of some patients, the numbers were too small to be of value to the evaluation. The organisms involved in these patients were similar to previous studies with Staph Aureus being the commonest. Adverse events were reported in 19/71 (27%)of the T and 14/61 (23%) of the V patients; those of significance, taking into account the nature of the study population, are shown in Appendix 7. Other than the haematological ADR seen with T , as opposed to V, the patterns were similar. Again numbers are small.

As mentioned at the outset, it is not really possible to draw any conclusions of import from this study.

PROTOCOLS 102 -001 and 102 -002. VOLUME 93 - PAGE 17712 APPENDIX 8.

TITLE: - An early Phase II efficacy and safety study of teicoplanin in patients with Gram-positive infections.

An early Phase II study with small numbers of patients (Appendix 8) designed primarily to assess efficacy and safety. As shown in Column 5 of Appendix 8, there were 6 subsets amongst the total of 51 patients. With such small numbers the significance of the study, seen by the Sponsor as non-pivotal, is not that great. It did however show that 74% of the patients were cured/improved with 69% of the organisms being eradicated.However, doses used were amended beyond the PI recommendations. Adverse drug reactions were similar to those in previously discussed larger studies.

PROTOCOL 102 - 013 - 2. VOLUME 95 - PAGE 18216.

TITLE:- An open study of teicoplanin in the treatment of intravenous drug abuse associated endocarditis caused by Gram-positive bacteria.

This study recruited 18 patients of whom only 7 bacteraemic patients were treated for > 5 days. The mean duration of treatement was but 5.2 (2 - 17) days. It is thus not possible to adequately assess efficacy. The contribution of this study is the demonstration that patients tolerated i.v. teicoplanin 30 mg/kg 12 hourly for 3 doses followed by 30 mg/kg 12 or 24 hourly. Three patients had chills with nausea; with one being discontinued due to nausea.

PROTOCOL TEIC/86/12/1. VOLUME 96 -PAGE 18422. APPENDIX 9.

TITLE: - A randomised, blinded comparative study of teicoplanin versus vancomycin in the treatment of infections caused by Methicillin - resistant Staphylococci.

This is an important study in as much that it looked specifically at the efficacy of T and V against MR Staphylococci. It's limitation which has rendered it, in the Sponsor's opinion, to a non-pivotal study, relates to difficulties in recruitement aimed at 200 patients. After 4 years only 98 patients had been entered and the study was closed. Of the 98 patients, the only substantial group was that of 55 patients with cellulitis (T 31, V 24). Despite this, as summarised in Appendix 9, it was shown that T and V were equally effective in the treatment of MR Staphylococci. The most significant laboratory changes were significant decreases in WBC and neutrophils with both T and V.

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REMAINING ASPECTS OF THE ASSESSMENT REPORT.

1. PREGNANCY: there was no data on the use of teicoplanin in pregnancy in the data reviewed, largely because pregnancy was an exclusion for all the studies.

2. POST MARKETING EXPERIENCE: some relatively recent literature has been reviewed in this regard:

Teicoplanin was generally reviewed by Phillips and Golledge (1). Microbiologically, in comparison with vancomycin, both agents are restricted in usefulness to Gram - positive aerobic and anaerobic bacteria. Their activity is not identical with T more active against Streptococci and Gram-positive anaerobes, equally active against Staph. Aureus (including MR Staph.) and less active than V against some strains of coagulase negative Staph (2). Whilst evidence of resistance is scant, some enterococci have been reported to show resistance to T (3).

Three published studies are briefly presented:

a.) Davey and Williams (4) have reviewed patients treated with T monotherapy for endocarditis or Staph. Aureus bacteraemia. All the patients with streptococcal endocarditis were cured (18/18)- 3.5 to 9.5 mg/kg, Enterococcus faecalis (3/5) - 3 to 8 mg/kg, Staph. Aureus (5/10)- 3.3 to 12.2 mg/kg and coagulase negative Staph (2/3). Doses for the 6 failed patients were 3.3 to 4.2 mg/kg/day. Of patients with Staph.Aureus bacteraemia 41/48 were cured and 2 failed due to ADRs. It was concluded that T monotherapy is effective in serious infections with Gram-positive bacteria and with Staph. Aureus the dose should be > 6 mg/kg/day.

b.) Schmit (5) reviewed data on 63 cases of enterococcal infection (endocarditis 18, septicaemia 8, urinary tract 29, skin/soft tissue 6 and bone/joint 2) of whom 48 were treated with T monotherapy and 15 with T and an aminoglycoside. The clinical cure rate was 84%, 5% improved, 8% had a clinical recurrence and 3% did not respond. Bacteriological eradication = 87%. There was no difference in response between monotherapy and combined therapy.

c.) Cruciani et al (6) reviewed the use of i.v. T in patients with Staphylococcal neurosurgical shunt infections using intraventricular therapy ranging from 5mg/day (infants), 20 mg/day (adults). The mean duration of treatment was 16 days with CSF becoming sterile on average after 4.4 days. All patients cured and there were no reported side effects.

Finally, turning to safety. Davey and Williams (7) reviewed data in 3377 patients treated in Europe up to July 1990. One or more ADR was noted in 10% of patients (n = 347).

Allergy	89.
Altered LFT	57.
Pyrexia	27.
Local intolerance	55.
Ototoxicity	11.
Altered renal function	22.
Miscellaneous	86.

There was no relationship to age or dose. It is felt that T is less toxic than vancomycin in terms of ototoxicity and skin reactions, where there is no evidence of histamine release with teicoplanin (8).

3. PRODUCT INFORMATION: overall, this reflects the data accurately, although there are a number of problems especially with regard to dosage. The following suggestions are proposed:

Page 164: - " One step resistance to teicoplanin has not been obtained in vitro. " In view of the possibility of some resistance amongst enterococci (3), perhaps this might be modified slightly.

Page 166: - 1.) ADR -Looking at the discussion of side effects, would it be worth providing some numerical idea of frequency of the common ADRs e.g. rash, fever, pruritis.

2.) Dosage and administration - as alluded to earlier in the evaluation, most of the studies evaluated (see pages 10,12,16,17 and 20) have used or have ended up using, doses greater than recommended in the PI. It is stated in the PI that the dose should be increased in " life threatening " conditions which in most situations osteomyelitis and septic arthritis would not be considered as, yet the dose used in these patients was above the recommended maintenance dose of 3 mg/kg.

Page 167: -

1.) Children: the evaluator is unclear as to the validity of the PI recommended doses, for as already suggested, the paediatric studies are probably the weakest component of this submission. Further the pharmacokinetic date is difficult to follow with the much abbreviated half life in children and especially neonates which is contrary to what is usually seen in the neonatal period for renally excreted drugs. There is possibly a need for further paediatric studies, in terms of kinetics, use in sick patients rather than largely as prophylaxis and perhaps in terms of safety.

2.) Duration of therapy: there is little information in this regard other than to say that this should be assessed clinically (which is quite correct) and that in endocarditis and osteomyelitis it should be for 3 weeks or longer. As T is a parenteral preparation, it would presumably only be given to persons with significantly serious infections and perhaps more specific information might be provided whilst accepting the correctness of judging the end result clinically. Suggestions are:

* Superficial infections - 7 to 10 days.
* Uncomplicated bacteraemia - 10 to 21 days.
* Endocarditis and osteomyelitis - 3 to 6 weeks.

3.) More specific information is required as to when T might be given i.m. As Cmax is lower than with iv dosing, it should not be used initially or in seriously ill patients especially in the presence of shock or hypovolaemia. It might thus be suggested that the i.m. route would be suitable for maintenance therapy after Day 3 or 4, depending upon the clinical situation.

4.) It is stated that in endocarditis, treatment should be for > 3 weeks, but there is no recommendation of increased dosage which has been demonstrated in all the studies evaluated.

5.) A dose of 6mg/kg/day should be recommended for those with complicating illnesses such as diabetes or cardiovascular disease (see page 15.)

6.) " Renal impairement " - the term in the second line " the first FEW days " might be made more specific. The term "few " is open to interpretation.

4. CONCLUSIONS AND RECOMMENDATIONS.

Teicoplanin is a relatively simple, non-metabolised compound with a prolonged half life permitting once daily dosage and an ADR profile accepted in the glycopeptide group and perhaps slightly less than vancomycin.

The data has shown teicoplanin to be effective in the often very difficult clinical situations in which it was studied. Indeed, the complex medical and social nature of many of the patients may have made the studies more difficult to perform and assess than otherwise might have been the case. The submitted data has defined dosage as effectively as can be the case for an antimicrobial, although this evaluator has some concerns about paediatric dosage studies and thus dosage recommendations. The concerns are not sufficient to impede marketing, but as suggested on pages 23 and 24, there are some matters, especially with respect to dosage and duration of therapy that need to be considered.

The data suggests that teicoplanin is as effective as currently accepted therapy - Vancomycin - in terms of efficacy and has a slightly better side effect profile. There was no tangible data on the safety profile of T in patients who had vancomycin ADRs, nor was there data on T efficacy in vancomycin resistant cases, but there was good data on methicillin resistant cases. Overall, the safety profile is acceptable taking into account the nature of the illnesses being treated. The data in the elderly and in renal impairment is good and there is adequate pharmacokinetic data.

This evaluator sees no clinical or bacteriological impediment to marketing, although paediatric issues, dosage recommendations and information on the duration of therapy need to be resolved.

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7.) Davey PG and Williams AH. A review of the safety of teicoplanin. J. Antimicrob. Chemother. 1991, 27, Suppl B, 69 - 73.

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27.

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SECTION B.

SUMMARY OF PHARMACOKINETIC AND CLINICAL DATA.

APPENDIX 1/1

TARGOCID - SUMMARY OF PHARMACOKINETIC AND BIOAVILABILITY DATA

B 3 Study	Design	Subjects No. Age. Sex	Dose Duration	Route Form	Pharmacokinetic Data					ADR, Drop outs, Safety	Conclusions/Comments
					Cmax mg/l	Vd l/kg	AUC mg/h/l	t1/2 hours	CLr ml/h/kg		
MILAN B3 1/35 Ref (1)	Single Dose	VOLUNTEERS 5, M, 25-40 y	2mg/kg Single Dose	I.V. over 30 min.	15.7	0.68 ± 0.1	107.6 ± 10.1	31.9 ± 6.8	18.8 ± 1.8	No ADR NOTED	MICROBIOLOGICAL ASSAY. SAMPLES COLLECTED TO 96 HOURS.
		5, M, 21-28 y	3mg/kg		22.4	0.84 ± 0.23	187.9 ± 32.2	49.1 ± 21.7	16.4 ± 2.5		
LEUVEN B3 1/14 Refs (2 & 3)	Single Dose Triple Randomised Crossover.	VOLUNTEERS Male 22 - 23 y 6	Single Dose 3mg/kg	I.V. over 5 min.	53.5 ± 22.3	* 59.2 ± 8.7	265.5 ± 39.9	47.4 ± 8.5	7.67 ± 1.0	I.V. No ADR	MICROBIOLOGICAL ASSAY. * Vd expressed in litres NOT l/kg
		6	6mg/kg	I.V. over 5 min.	111.8 ± 43.4	55.1 ± 6.6	520.9 ± 101.1	44.1 ± 5.6	7.6 ± 1.4	I.M. 4/6 Volunteers had local pain up to 12 hours.	SAMPLES COLLECTED TO 102 HOURS. I.M. BIOAVAILABILITY = 0.94 0-3 TMAX = 2.0 ± 1.2 HRS.
		6	3MG/KG	I.M.	7.12 ± 1.8	68.9 ± 11.7	231.1 ± 54.1	47.5 ± 5.8	7.98 ± 1.3		
PAVIA B3 2/193 Ref (4)	Single Dose ↓ 7 Day Gap ↓ Multiple Dose	VOLUNTEERS 8, M, 22 - 41 y	400mg Single Dose	I.V. over 1 minute	71.0 ± 1.75	0.71 ± 0.03	553 ± 16	70.2 ± 1.6	5.86 ± 0.4	None Including Audiometry	* = 0 - 24 hours MICROBIOLOGICAL ASSAY Samples Collected to 169 hours. ** Kinetic Data Obtained after last dose
			400mg Daily for 6 Days **		74.1 ± 4.9	--	368* ± 12	69.3 ± 2.2	6.4 ± 0.4		

TARGOCID - SUMMARY OF PHARMACOKINETIC AND BIOAVAILABILITY DATA

B 3 Study	Design	Subjects No. Age. Sex	Dose Duration	Route Form	Pharmacokinetic Data					ADR, Drop outs Safety	Conclusions/Comments
					Cmax mg/l	Vd l/Kg	AUC mg/h/l	t1/2 hours	CLr ml/h/kg		
PAVIA B 3 2/299 Ref (6)	Multiple Dose	VOLUNTEERS 8, M, 23 - 40 y	6 doses of 200 mgs over 5 days (12 hourly for first 3 doses)	I.M.	(Day 1) 7.1 ± 0.81	--	--	98.7 ± 2.8	11.6 ± 0.7	No ADR other than local pain with first 3 injections.	MICROBIOLOGICAL ASSAY. SAMPLES COLLECTED UP TO 20 DAYS. TMAX (DAYS 1 & 5) = 4 ± 0.8L CMAX (DAY 5) = 12.1 ± 0.9
PERUGIA B3 3/387 Ref (14)		VOLUNTEERS 5, M, 24 - 34 y	14C 400 mg Labelled Single dose	I.V.	--	0.83 ± 0.06	533.2 ± 43.0	90.5 ± 3.3	7.8 ± 0.6		SAMPLES COLLECTED TO 16 DAYS & 80% OF DOSE RECOVERED IN THE URINE
U.K. B3 3/431 Ref (15)	Cantharides Induced Blisters	VOLUNTEERS 6, M, 20 - 28 y	440mg Single Dose	I.V.	--	--	--	--	--		I.V. KINETICS UNSUITABLE AS SAMPLING TIME (48 HRS) TOO SHORT. BLISTER FLUID PENETRATION GOOD REACHING 77% OF SERUM CONCENTRATION. BLISTER C MAX 14.8mg/l at 2.7 HOURS.
LYON B3 4/545 Ref (26)	Kinetic Study	RENAL FAILURE 6 VOLUNTEERS 3F, 3M, 28 - 62 y	3mg/kg Single Dose	I.V. over 2 - 3 mins.	—	1.13 ± 0.17	197 ± 15	62 ± 5	9.3 ± 0.8		HPLC ASSAY SAMPLES COLLECTED TO 120 HOURS. 3 COMPARTMENT MODEL
		*Moderate R.F. (Creat Cl 57.0 + 3.5ml/ 2F, 4M, 40 - 65 y			—	1.11 ± 0.13	326 ± 42	96 ± 19	3.2 ± 0.5		
		*Severe R.F. (Creat Cl 9.9 + 1.4 ml/ 3F, 3M, 36 - 74 y			—	1.17 ± 0.17	409 ± 72	111 ± 15	0.6 ± 0.1		

APPENDIX 1/3

TARGOCID - SUMMARY OF PHARMACOKINETIC AND BIOAVAILABILITY DATA

B 3 Study	Design	Subjects No. Age. Sex	Dose Duration	Route Form	Pharmacokinetic Data					ADR. Drop outs Safety	Conclusions/Comments
					Cmax mg/l	Vd l/kg	AUC mg/h/l	t1/2 hours	CLr ml/h/kg		
MILAN B 3 4/677 Ref (28)	OPEN KINETIC STUDY	29 PATIENTS RENAL FAILURE 21M 30 - 78y. 5 Groups a/c to Creat Cl. * 30 - 80 ml/min * 10 - 29 ml/min * 3 - 9ml/min * < 2ml/min on CAPD * < 2ml/min on Haemodialysis * 5 Volunteers Male 21 - 28 y	3mg/kg Single Dose	I.V.	— — — — — —	0.89 ± 0.22 0.95 ± 0.18 1.02 ± 0.35 1.16 ± 0.33 — 0.84 ± 0.23	326 ± 63 385 ± 78 514 ± 127 607 ± 172 — 188 ± 32	75 97 124 157 — 41	10.3 ± 2.2 10.2 ± 2.5 6.8 ± 2.0 5.7 ± 2.0 — 18.9 ± 4.1	NO ADR	MICROBIOLOGY ASSAY SAMPLES COLLECTED OVER 168 HOURS. * CAPD BARELY AFFECTED KINETICS * WITH HAEMODIALYSIS, WHERE TEICOPLANIN WAS MEASURED IN DIALYSATE, ONLY TRACES WERE DETECTED
MILAN B 3 4/703 Ref (29)	OPEN KINETIC STUDY	RENAL FAILURE C.A.P.D. 4 M, 1 F 44 - 74 y	3mg/kg Single Dose	I.V.	—	1.16 ± 0.32	607 ± 172	186 ± 9.5	—		MICROBIOLOGY ASSAY SAMPLING FOR 7 DAYS Dialysate Concentration Very Low, So Recommended for the Treatment of Peritonitis, to Add Teicoplamin to Dialysis Fluid

TARGOCID - SUMMARY OF PHARMACOKINETIC AND BIOAVAILABILITY DATA

B 3 Study	Design	Subjects No. Age. Sex	Dose Duration	Route Form	Pharmacokinetic Data					ADR, Drop outs Safety	Conclusions/Comments
					Cmax mg/l	Vd l/kg	AUC mg/h/l	t1/2 hours	CLr ml/h/kg		
PAVIA B3 5/747 Ref (32)	OPEN KINETIC	ELDERLY 12 Patients 7M, 65 - 81 y N.B. Mean Creat Cl = 51.3ml/hr/kg	6mg/kg Single Dose	I.V. Over 3 - 5 minutes	—	1.7 ± 0.2	607 ± 37	114.3 ± 8.6	—	NO ADR	MICROBIOLOGY ASSAY * Sampling to 192 hours * Simulated Multiple Dosing Suggested 3 daily doses of 6mg/kg, then 4mg/kg every second day for trough level of 5.6mg/l.
GENOA B 3 5/786 Ref (33)	OPEN KINETIC	CHILDREN 14 Patients Boys 2 - 13 y	3mg/kg Single Dose	I.V. over 3 - 5 minutes	—	1.25 ± 0.1	208.3 ± 5.1	58.2 ± 3.8	14.7 * ± 0.4	NO ADR	* =TOTAL BODY CLEARANCE MICROBIOLOGY ASSAY * Sampling to 192 hours * Multiple Dosing Simulation = 6mg/kg daily for 3 days & then 4mg/kg/day → trough of 7mg/l
STRASBOURG B 3 5/826 Ref (34)	OPEN KINETIC	CHILDREN 6 girls, 4 - 12 y NEONATES 4 Full Term Babies * 2 F aged 3 days (3.35 & 3.2kg) * 2 M Aged 2 & 25 days (2.7 & 3.8kg)	6mg/kg Single Dose " " "	I.V. over 10 minutes I.V. over 20 minutes	— —	0.54 ± 0.17 0.61 ± 0.07	— —	20.4 ± 5.4 30.3 ± 6.6	28.2 * ± 5.8 15.8 * ± 3.1	NO ADR	* =TOTAL BODY CLEARANCE ML. $L.^{-1}$ Kg^{-1} · HPLC Assay · Sampling for 10 days DIFFICULT STUDY TO ASSESS AS A 2 COMPARTMENT MODEL WAS USED - ALL OTHERS USED 3 COMPARTMENT MODEL, WHICH FITS DATA BETTER

APPENDIX 2

OPEN STUDY OF TEICOPLANIN IN THE TREATMENT OF I.V. DRUG ABUSE ASSOCIATED ENDOCARDITIS CAUSED BY GRAM - POSITIVE BACTERIA

Name of finished product: TARGOCID Name of active ingredient(s): TEICOPLANIN				Summary of Clinical Trials referring to Page 10 of "Assessment Report" NON CONTROLLED STUDY				Criteria for evaluation	Results (efficacy) 40 Evaluable	Adverse Reactions 80 Evaluable
Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.			
Protocol 102/013 Vol 7 p 1191	Phase II Multicentre Study 13 U.S. Centres Co-ordinated by Sponsor	Open and Non - Comparative	82 Patients M 45, F 37 24 - 64 y 40 Evaluable for Efficacy 82 Evaluable for Safety	Positive Blood Culture + Clinical & Diagnostic Imaging of Endocarditis	Non-Cardiac Bacteraemia 3-4 weeks Endocarditis 4-6 weeks Maximum 10 weeks	200 mg 6mg/kg/12 hours for 3 doses ↓ Protocol Amendments over 2 years to 30mg/kg dose at 0, 12, 24 hrs & then 15mg/kg/12hrs for Staph Endocarditis and 6-15mg/kg/day for non-Staph Endocarditis		Safety Assessed by Haematology & Biochemical Assessments on Days 0, 3, 10 & weekly. Daily Clinical Assessment & Audiometry on Days 0, 10 & weekly. Efficacy - Assessed Clinically & by Recurrent Blood Cultures	9 NON-CARDIAC BACTERAEMIA All cured / improved with Bacteriological Elimination. 4 Staph-Aureus 5 Streptococci 31 CARDIAC BACTERAEMIA 20 cured or improved. 15 Staph-Aureus 5 Streptococci 9/11 Clinical Failures were infected with Staph Aureus & 2/11 stretpococci	Rash - 9 Fever - 6 Pruritis - 2 Angioedema - 1 SGOT ↑ -18/61 SGPT ↑ -14/57 AlkPhos↑ - 5/61 Creat ↑ - 3/60 Audiometry↓- 1 Platelets ↓- 3/61 WBC ↓ - 5/63 Neutropenia- 6/53 18/80 Discontinued Due to ADR.

APPENDIX 3

RANDOMISED, BLINDED, COMPARATIVE STUDY OF TEICOPLANIN V VANCOMYCIN IN THE TREATMENT OF NON-VASCULAR ACCESS ASSOCIATED BACTERAEMIA/ENDOCARDITIS BY GRAM - POSITIVE BACTERIA

Name of finished product: TARGOCID Name of active ingredient(s): TEICOPLANIN				Summary of Clinical Trials referring to Page 12 of "Assessment Report" CONTROLLED STUDY WITH REFERENCE THERAPY				Criteria for evaluation	Results (efficacy)	Adverse Reactions
Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment (DAYS)	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.		(n = 52)	106 EVALUABLE
Protocol 102/014 Vol 14 p 2471	25 U's Centres Co-ordinated by Sponsor	Randomised Double Blind TEICO (T) v VANCO (V)	106 Entered T n = 50 M 37 Age 50 ± 17 V n = 56 M 35 Age 54 ± 21	Clinical Observation, Positive Blood Cultures + Diagnostic Imaging of Cardiac Involvement	<u>Bacteraemia</u> T = 17.2 ±2.1 V = 25.2 ± 5.8 <u>Endocarditis</u> T = 23.9 + 4.2 V = 19.6 ± 3.1 (± = S.E)	200 mg 6mg/kg/12 hours for 3 doses → 6mg/kg/day I.V. Adiostments for Renal Dysfunction & Blood Levels As Study Progressed→ Increased Doses in Staph Endocarditis ↓ Aim at Trough Levels of 25mg/l Max. dose of 30mg/kg/day	15mg/kg/12 hours I.V. (500mg vial) FOR ←BOTH→ DRUGs	Daily Clinical & Bacteriological Assessment → Sterile Cultures + Clinical Cure or Improvement Follow-up Clinically & for Bact. Relapse	<u>NON-CARDIAC BACTERAEMIA</u> T = 11/13(84%) Cured / improved V = 13/19(68%) Cured / improved <u>ENDOCARDITIS</u> T = 3/14(21%) cured / improved V = 5/6(83%)	EVALUATED FOR SAFETY (See text for Comments) T V Fever 0 1 Rash 1 3 Urticaria 1 0 Nephropathy 0 1 Ac Renal F 0 1 Hearing ↓ 0 1 Tinnitus 0 1 Neutropenia 0 2 Thrombo-cytopenia 1 0

APPENDIX 4

A RANDOMISED OPEN STUDY OF TEICOPLANIN V CEFAZOLIN IN THE TREATMENT OF MODERATE TO SEVERE SKIN & SOFT TISSUE INFECTIONS CAUSED BY GRAM - POSITIVE BACTERIA

Name of finished product: TARGOCID
Name of active ingredient(s): TEICOPLANIN

Summary of Clinical Trials referring to Page 13 of "Assessment Report"
NON CONTROLLED, COMPARATIVE STUDY

Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.	Criteria for evaluation	Results (efficacy)	Adverse Reactions For Teicoplanin
Protocol 102/007 Vol 23 p 3935	Multicentre. 39 Investigators U.S.A. Co-ordinated by Sponsor	Open Randomised V Cefazolin Also Non-Random Arm	RANDOMISED 418 Enrolled with Evaluable for Efficacy T.I.M. = 82 T.I.V. = 106 Cefazolin V. = 105 Sex F 99 M 319 Age 52 ± 17 NON-RANDOMISED 262 Enrolled & 181 Evaluable for Efficacy Sex F 90 M 172 Age = 50 ± 17	Clinical Cellulitis, Furunculosis, Carbuncles, Tissue Abscesses, Surgical or Traumatic Wound Infection and Gram Positive Cultures	All Groups on Average. 8 - 12 Days (Max. 28 Days)	200 mg & 400mg I.V. 6mg/kg/load → 3mg/kg/day ↓ Amended Protocol ↓ 12mg/kg load → 6mg/kg/day Two Groups I.M. = 125 I.V. = 148	I.V. Cefazolin 500 - 1000mg 6-8hrly N= 140	* > 5 Days Treatment * Clinical Cure / Improvements * Bacteriological Elimination Sought	See Assessment Report (Page 14)	Randomised N = 273 Non-Randomised N = 281 Hypersensitivity Rash 28 Fever/Chills 20 Pruritis 10 Eosinophilia 5 Hepatic Enzymes ↑ 12 Renal Creat ↑ 2 B.U.N. ↑ 1 CASTS 1 Hearing Tinnitus 4 Dizziness 8 Vertigo 1 Haematology WCC ↓ 4 Platelets ↓ 4

APPENDIX 5

A RANDOMISED, BLINDED, COMPARATIVE STUDY OF TEICOPLANIN V VANCOMYCIN IN THE TREATMENT OF VASCULAR ACCESS ASSOCIATED BACTERAEMIA/SEPTICAEMIA CAUSED BY GRAM-POSITIVE BACTERIA

Name of finished product: TARGOCID
Name of active ingredient(s): TEICOPLANIN

Summary of Clinical Trials referring to Page 15 of "Assessment Report"
CONTROLLED STUDY WITH REFERENCE THERAPY

Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.	Criteria for evaluation	Results (efficacy)	Adverse Reactions Evaluable = 238
Protocol 102/009 Vol 52 p 9601	Multicentre 49 Investigators U.S.A. Co-ordinated by Sponsor	Randomised Blinded Study Comparing Teico. to Vancomycin	ENTERED T = 118 M 76, F 42 Age 50 ± 19 V = 122 M 73, F 48 * Age 52 ± 19 Evaluable for Efficacy T = 60 V = 64 * 1 Missing	Clinical Evidence of Erythema, Pain, Tenderness within 2cm of exit of Catheter + Gram-Positive Blood Cultures	Average = 10 days for both Drugs	400mg & 200mg I.V. 3 Load Doses of 6mg/kg/12 H ↓ Alternate with Placebo * at 6mg/kg/12 hrly Suspected Staph Endocarditis Loaded with 9 Doses of 6mg/kg/12 hrly Average Dose = 6.9mg/kg/day	500mg vial I.V. 12mg/kg /12hr As 60 min infuson Average Dose 21.4mg/ kg/day	* Daily Clinical and Bacteriological Assessment. * Blood Cultures Daily x 5 & then Weekly. * > 5 Days Therapy * 1 - 4 Weeks Post Therapy Follow-Up. * Seeking Cure or Improvement	T 48/60 (80%) Cure / Improvement with 46/48 Bacterial Elimination. V 51/65 (80%) with 51/53 Bacterial Elimination	T 117 V 121 Rash 8 4 Prutitis 3 3 Flushing 0 1 Red Man Synd. 0 1 Fever 3 2 Liver Enzymes ↑ 2 3 Creat ↑ 2 3 Hearing ↓ 2 0 Eosino-phil ↑ 1 1 WBC ↓ 2 0 Platelets ↓ 2 0

* AS VANCOMYCIN WAS GIVEN 12 HOURLY AND T ONCE DAILY, PLACEBO WAS USED FOR ALTERNATING T DOSES SO AS TO MAINTAIN BLINDING.

APPENDIX 6

AN OPEN STUDY OF TEICOPLANIN IN THE TREATMENT OF ACUTE BONE AND JOINT INFECTIONS CAUSED BY GRAM - POSITIVE BACTERIA

Name of finished product: TARGOCID
Name of active ingredient(s): TEICOPLANIN

Summary of Clinical Trials referring to Page 17 of "Assessment Report"
NON CONTROLLED STUDY

Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.	Criteria for evaluation	Results (efficacy)	Adverse Reactions
Protocol 102/012 Vol 64 p 12154	Multicentre U.S.A. 34 Investigators Co-ordinated by Sponsor	Open	342 PATIENTS ENTERED Acute Osteo = 137 M 94 Age 50 ± 17 Chronic Osteo = 129 M 89 Age 49 ± 18 Septic Arthritis = 75 M 53 Age 49 ± 21 220 EVALUABLE FOR EFFICACY 90 Acute Osteo 79 Chronic Osteo 51 Septic Arthritis	Acute or Chronic Osteo or Septic Arthritis * Clinical Diagnosis * Aspiration Cultures * Diagnostic Imaging	Septic Arthritis ± 4 weeks Osteomyel-itis ± 6 weeks Max 10 weeks	200mg & 400mg 3 Dosage Schedules * 6mg/kg/day amended to 12mg/kg/day * Load 6mg/kg/12hr for 3 doses amended to 12mg/kg/12hr & Maintenance of 6mg/kg/day for Osteo or 12mg/kg/day for Septic Arthritis I.V. 30 min Infusions of I.M.		* Daily Clinical & Bacteriological Assessment * > 5 Days Treat * 4 Week Follow up Septic Arth * 6 Month Follow up - Osteo Cure = Complete Clinical and Bacteriological Results over 2 - 3 Weeks with no Recurrence	* Acute Osteo 90% * Chronic Osteo 89% * Septic Arthritis 82% I.M. used as Out-Patient Therapy in Late Stages of Therapy Were Effective	Please See Text. Page 18.

APPENDIX 7

MULTICENTRE, RANDOMISED, BLINDED, COMPARATIVE STUDY OF TEICOPLANIN DOSING REGIMENS & VANCOMYCIN IN THE TREATMENT OF ENDOCARDITIS & BACTERAEMIA OF NON-CARDIAC ORIGIN CAUSED BY GRAM-POSITIVE BACTERIA

Name of finished product: TARGOCID
Name of active ingredient(s): TEICOPLANIN

Summary of Clinical Trials referring to Page 19 of "Assessment Report"
CONTROLLED STUDY WITH REFERENCE THERAPY

Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment (DAYS)	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.	Criteria for evaluation	Results (efficacy) 62 Evaluable	Adverse Reactions 132 Evaluable
Protocol 102/019 Vol 85 p16288	Multicentre U.S.A. 19 Investigators Co-ordinated by Sponsor	Randomised Blinded Comparing TEICO to VANCOMYCIN	132 Entered ↓ 62 Evaluable for Efficacy 132 for Safety T = 71 M 52 F 19 Age 44 ± 15 V = 61 M 45 F 16 Age 42 ± 16	Clinical & Laboratory Diagnosis + 2 Gram-Positive Blood Cultures + in Endocarditis Imaging Evidence of Cardiac Involvement	Bacteraemia T 13 ± 1.5 V 11.3 ± 3.1 Endocarditis T 24.2 ± 3.1 V 24.8 ± 2.1	400mg I.V. 30mg/kg/load at 0, 12, 24H → 30mg/kg/D alternating 12 hourly with Placebo (Saline) In Staph Aureus Endocarditis → 30mg/kg/12H Aiming at Trough Levels of 40 - 60mg/l	500mg vials Vanco-mycin 15mg/kg /12H. I.V.	* Daily Clinical and Bacteriological Assessment * Daily Blood Cultures x 7 till Negative & then Weekly * > 7 Days Treatment * Non-Cardiac Bacteraemia - Follow-Up 2 - 4 Weeks After Treatment * Cardiac Bacteraemia Follow-Up to 6 Months After Therapy	Clinical & Bacteriological Success. Bacteraemia T 20/23 (87%) Clinical & Bacteriological Success at 13 ± 1.5 days. V 12/13 (92%) Clinical, with 11/13 Bacteriological Success at 11.3 ± 3.1 days. Endocarditis T 5/9 (56%) at 24.2 ± 3.1 days V 15/17 (88%) at 24.8 ± 2.1 days. Follow-Up T 13 for 28.1 ± 5 days V 7 for 35.9 ± 9.0 days	Fever T 5 V 3 Rash 4 3 Pruritis 1 3 Liver Enzymes↑ 1 – Ac Renal Failure 0 1 Creat ↑ 1 0 Hearing ↓ 0 1 Tinnitus 1 0 Neutro-penia 2 0 Platelets ↓5 0

APPENDIX 8

AN EARLY PHASE II EFFICACY AND SAFETY STUDY OF TEICOPLANIN IN PATIENTS WITH GRAM-POSITIVE INFECTIONS

Name of finished product: TARGOCID
Name of active ingredient(s): TEICOPLANIN

Summary of Clinical Trials referring to Page 20 of "Assessment Report"
UNCONTROLLED STUDY

Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment (DAYS)	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.	Criteria for evaluation	Results (efficacy) 31 Evaluable	Adverse Reactions 51 Evaluable
Protocol 102/001 & 102/002 Vol 93 p 17712	8 Centres U.S.A. Co-ordinated by Sponsor	Open	51 Patients Entered 8 in 102/001 43 in 102/002 Data is Combined 31 Evaluable for Efficacy 51 - Safety 33 Male 18 Female 41.3 ± 15.4y	Clinical Infection + Gram-Positive Cultures Patients = 7 Bacteremia → 7 Endocarditis → 10 Bone/Joint → 19 Skin/Soft Tissues → 5 Chest Infection → 3 Miscellaneous →	→22 ± 9 →13.2 ± 7.7 →23.5 ± 12.3 →16.3 ± 15.6 →Uncertain →Uncertain	200 mg I.V. & I.M. 102/001 → 400mg IV/IM ↓ 200mg Daily 102/002 → 6mg/kg IV/IM ↓ 3mg/kg/Day Amended to 9mg/kg IV/IN ↓ 6mg/kg/Day Amended to 6mg/kg IV/IN Load and at 6 Hours ↓ 6mg/kg/Day		Clinical Cure OR Improvement & Bacterial Elimination	Cure = 12 (39%) Improved = 11 (35%) Failure = 4 (13%) Undetermined = 4 (13%) Bacteriology Staph Aureus = 27/31 inc 8 Methicillin Resistant Strain 69% Organisms Eliminated	9 Patients Reported 21 ADRS Injection Site Pain - 5 Fever - 5 Liver Enzymens Increased Transiently - 5 Neutropenia 2 Eosinophilia 2

APPENDIX 9

A RANDOMISED, BLINDED, COMPARATIVE STUDY OF TEICOPLANIN V VANCOMYCIN IN THE TREATMENT OF INFECTIONS CAUSED BY METHICILIN RESISTANT STAPHYLOCOCCI

Name of finished product: TARGOCID
Name of active ingredient(s): TEICOPLANIN

Summary of Clinical Trials referring to Page 21 of "Assessment Report"

Ref. Volume Page	Study -investigator -coordinating centre -centre(s) -report n	Design	No. of subjects with age and sex	Diagnosis + criteria for inclusion / exclusion	Duration of treatment	Test product dosage regimen route of administration formulation *	Ref. therapy Dose regimen route or admin.	Criteria for evaluation	Results (efficacy) n = 85	Adverse Reactions
Protocol TEIC 86/12/1	Multicentre 5 Centres Australia Co-ordinated by Sponsor	Randomised Blinded TEICO v VANCO	98 Entered 51 T 47 V Efficacy Numbers = T = 43 Male 27 60.2 ± 16.8y V = 42 Male 30 57.2 ± 21 y	Infections with M.R. Staphylococci * Cellulitis 55 Osteo 12 IV Line Sepsis 4 Septicaemia 4 U.T.I. 7 Chest Infections 3 * Cellulitis T = 31 V = 24	10 - 14 Days Except in Osteomyelitis = up to 6 weeks	200mg I.V. over 60 min 6mg/kg/12hrly for 3 doses ↓ 6mg/kg/day Alternating 12 hourly with Saline Placebo	Vancomycin 500mg I.V. over 60 min 15mg/kg /12 hrly	Clinical Cure or Improvement and Bacterial Elimination > 5 Days Treatment	Clinical Response Favourable T = 37/43 (86%) V = 41/42 (97.6%) * Bacteriological Teico Eliminated 62.8% Relapsed 2.3% Persistent 27.9% Uncertain 7% Vanco Eliminated 75.6% Relapsed 2.2% Persistent 11.1% Uncertain 11.1% * No Statistical Difference T & V p = 0.35	Reported ADRS T = 14 patients V = 11 patients Study Drug Related T = 3 patients (5.9%) V = 5 patients (10.6%)

SECTION C.

COMMENTS ON THE EXPERT REPORT.

COMMENTS ON THE EXPERT REPORT.

Overall, this evaluator felt that the expert report was a true reflection of the 98 volumes of data submitted.

INTENDED USE IN MAN (Volume C, page 19):

The need for a higher dose in endocarditis is mentioned here, but is not reflected in the PI. The same comments as already made pertaining to children apply to the information on page 20, Volume C.

The proposed population for use of teicoplanin is correct on the basis of the data submitted.

The matter of dosage has been dealt with earlier in this evaluation and again, the information on page 19 , Volume C, reflects a lower dosage that the studies would suggest.

APPRECIATION OF PHARMACOLOGY (Volume C, page 60):

There are no further comments to be made on this section which reflects the data submitted.

APPRECIATION OF CLINICAL DATA (Volume C, page 66):

This summary is as accurate as might be anticipated from the volume of data to hand, again bearing in mind the frequently difficult and ill patients studied. It confirms that T is as effective agent in the patients studied and as effective as V in similar clinical situations.

However, it demonstrates the need for higher doses than recommended in the PI in many of the seriously ill patients and those with complicating factors such as diabetes and cardiovascular disease. There was no evidence of significant drug interactions demonstrated, however this may have been difficult to evaluate taking into account the patient population and the numerous other medications that many of the were receiving. Despite this, there were no obvious interactions demonstrated.

ADVERSE REACTION DATA (Volume C, page 148).

Again, this data is complicated by the patient populations studies, especially the iv drug abusing patients who had many organ systems involved in their illnesses. Despite this, the summary accurately reflects the data submitted with hypersensitivity reactions (fever, chills and rash) being the main ADRs, sometimes severe enough for therapy to be ceased. Certainly the evidence would suggest T to be as safe, if not more so, than vancomycin.