AUSTRALIAN DRUG EVALUATION COMMITTEE

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The Managing Director
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Dear Sir/Madam

RE: TEICOPLANIN - TARGOCID

Please find enclosed copies of relevant edited extracts from the Minutes of Meeting No. 1993/6 (168th) of the Australian Drug Evaluation Committee and Minutes of Meeting No. 1993/6 (33rd) of the Pharmaceutical Subcommittee. These have now been ratified.

In due course, the ratified Minutes relating to the ADEC deliberations on this agenda item will be forwarded to the Chairman, Drugs and Poisons Schedule Standing Committee, for information and if appropriate, further action.

Yours faithfully

[redacted]

Section Head
ADEC Secretariat
General Administration Branch
~~February~~ 1994
March 1994

IN CONFIDENCE

EXTRACT OF RATIFIED MINUTES OF
THE 1993/6 (168th) MEETING
OF THE AUSTRALIAN DRUG EVALUATION
COMMITTEE 2-3 DEC 1993

ITEM 4.12 TEICOPLANIN - TARGOCID - MARION MERRELL DOW AUSTRALIA PTY LTD

4.12.1 The Committee considered evaluations of the data and Product Information submitted by Marion Merrell Dow Australia Pty Ltd in support of an application for registration of Targocid, lyophilised powder for injection containing teicoplanin 100mg/5mL, 200mg/10mL and 400mg/20mL.

Teicoplanin is a 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 teicoplanin is related to the vancomycin-ristocetin group of antibiotics.

The proposed 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, respiratory infections, skin and soft tissue infections, urinary tract infections and peritonitis associated with chronic ambulatory peritoneal dialysis. In addition, teicoplanin is indicated for prophylaxis in surgical patients in whom infection with gram-positive organisms would constitute a hazard (e.g. patients requiring cardiac, dental or orthopaedic surgery).

4.12.2 Teicoplanin is approved for marketing in 15 countries, including the United Kingdom and the Netherlands.

4.12.3 The 33rd meeting (1993/6) of the Pharmaceutical Subcommittee had considered the evaluations of pharmaceutical chemistry and quality control and had no objections to registration (Rec No 587). The PSC was concerned that an active degradation product (component A_3) was formed during the purification of teicoplanin bulk substance, but agreed to accept the finished product specification for teicoplanin on the basis of the sponsor's arguments.

4.12.4 The preclinical evaluator had noted that, by today's standards, the preclinical data were inadequate. The pharmacokinetic data in particular were poor, and there were limited secondary pharmacology studies. In addition, no studies on possible clastogenic effects of teicoplanin were conducted, despite requests by the TGA for this information. The kidney was the primary target organ for the toxic effects of teicoplanin, and there is evidence that the effect may be clinically relevant.

However, teicoplanin has similar properties to vancomycin, and may, in some cases, be of clinical advantage. The preclinical evaluator recommended that teicoplanin may be registered,

provided that its use is restricted to cases where vancomycin might be used. Preclinical approval was also based on the assumption that the clinical evaluator had assessed the issues associated with possible adverse renal effects, and that this was reflected in the Product Information.

4.12.5 The clinical evaluator had concluded that the presented data showed teicoplanin to be effective in the often very difficult clinical situations in which it had been studied. The evaluator had some concerns about the paediatric dosage studies and consequent dosage recommendations. There were no tangible data on the safety profile of teicoplanin in patients who had experienced an adverse drug reaction to vancomycin, nor were there data on teicoplanin efficacy in vancomycin resistant cases. The issue of the duration of therapy required resolution.

4.12.6 The TGA delegate noted that the quality of the submitted clinical and toxicology data left much to be desired. No evaluable efficacy or safety data had been provided concerning use in children. Kinetic data in children were contrary to physiological expectations. Dosage regimens used in the clinical trails appeared to have changed frequently, and optimum dosages remained unclear. Information concerning duration of treatment in the clinical trials was confused and inadequate. No data were provided to define a population which could be treated appropriately by the intramuscular route. The proposed dosage regimen for patients with impaired renal function had not been justified with supporting evidence. No efficacy data had been provided for a number of the proposed indications.

The delegate proposed two options for consideration by ADEC.

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 β-lactam antibiotics:

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

4.12.7 The Committee reviewed the key issues identified in the evaluations.

(1) The preclinical evaluator had noted that *in vivo*, in animal studies, teicoplanin had only demonstrated efficacy with methicillin resistant Staphylococci, *Streptococcus pyogenes* and *Streptococcus pneumoniae*.

(2) Teicoplanin is microbiologically active against gram-positive aerobes, particularly methicillin resistant staphylococci, Group D streptococci including Enterococcus faecalis, and Corynebacterium Group JK. It is also effective against Clostridium difficile.

(3) It is very like vancomycin. It has a fatty acid moiety which makes it more lipophilic than vancomycin and it therefore might be expected to have greater tissue penetration. It was hoped from initial work that there would be fewer adverse reactions than with vancomycin. In particular, it is less likely to produce a histamine-like release (Red Man syndrome) and perhaps less nephrotoxicity and ototoxicity.

(4) There were stillbirths in puppies but no teratogenesis.

4.12.8 The clinical evaluator had noted that after a single dose the C_{max} was 7μg/mL. To attain reasonable concentrations at the initiation of therapy, a loading dose needs to be given. The dosages were ascertained to some extent as the trials continued. Teicoplanin is 90% protein bound in comparison with vancomycin, which is 55% protein bound, and has a longer half life (up to 100 hours). The presented data are fairly inadequate in children. Half life varied between 20-60 hours in boys and girls and was about 30 hours in neonates. It has poor CSF penetration, but clinically potentially useful penetration into bone, joint fluids and lung.

4.12.9 A Member noted that there were minimal data on pharmacokinetics in neonates, children and the elderly. The fact that teicoplanin may cause renal dysfunction and adjustment of the dose in renal failure is not necessarily based on efficacy studies make dosage recommendations difficult. This is coupled with the fact that the company does not recommend monitoring serum concentrations of the drug. Teicoplanin is a drug for which monitoring of serum levels should be required. The Product Information should advise users to measure serum concentrations so that an appropriate therapeutic range can be elucidated and more precise parameters for toxicity established. The delegate noted that some information was provided in the table of adverse rections in the Product Information.

4.12.10 Another Member added that the guidance on plasma monitoring in the Product Information is not very helpful. It simply says (for children) that trough serum concentrations should be greater than 10μg/mL. The UK Product Information speaks of monitoring in terms of efficacy, rather than in terms of toxicity, which was the major concern. There were few data presented on the use of this agent in patients with liver dysfunction. Drug interaction data were also limited.

4.12.11 In the endocarditis trials, the clinical evaluator had reported that initial dosages were 6mg/kg in the two pivotal studies. The dose was 6mg/kg 12 hourly for three doses, and then 3-6mg/kg 12 hourly. During the course of the trial, it became necessary to increase the doses to 30mg/kg 12 hourly, later reduced to 15mg/kg for staphylococcal infections, because of early failure rates. The dose was maintained at 6-15mg/kg for non-staphylococcal endocarditis. There were an alarming number of failures in the early stages of the endocarditis trials e.g. 11 failures from 31 patients in the 013 trial. In the 014 trial in which teicoplanin was compared with vancomycin, 3 of 14 patients were cured using teicoplanin, and 5 of 6 using vancomycin. After the change in dose, efficacy increased but it was still not as good a drug for treating endocarditis as vancomycin. In some of the non-pivotal trials, the summary showed 56% efficacy for teicoplanin as opposed to an 88% efficacy for vancomycin. The studies were really dose-ranging as well as tests of efficacy.

A Member considered that teicoplanin was definitely inferior to vancomycin for treating staphylococcal endocarditis, particularly in the light of the fact that most of the patients with staphylococcal endocarditis were drug users with presumed right sided endocarditis which is much easier and simpler to treat than left sided endocarditis.

4.12.12 For skin and soft tissue infections, the clinical evaluator had reported on one pivotal and 2 non-pivotal trials. In the pivotal trial, teicoplanin was compared against cefazolin, a first generation cephalosporin. Efficacy was comparable to that of cefazolin. The cure rates when teicoplanin was administered by the intravenous route were 95-97%, and it gave better bacterial elimination than cefazolin. There was a high percentage of patients with cardiovascular disease and diabetic patients in the trial, in whom one would expect to see a high proportion of staphylococcal infections, in particular. In the non-pivotal trial, teicoplanin was as efficacious as vancomycin.

The pivotal study used other antibiotics together with teicoplanin. It could be argued therefore that there were no valid comparative studies. However, the trialists chose the antibiotics carefully so as not to have any gram-negative activity. Aztreonam and metronidazole were used when needed. The presenter considered that their use did not necessarily detract from the value of the trial.

4.12.13 The TGA delegate pointed out that for many years the company had tried to include a variety of infections not strictly related to the skin and skin structure under the heading of "soft tissue infections". In the USA, the wording "skin and skin structure infections" is now used. The Committee disagreed strongly with the company's inclusion of cellulitis, urinary tract infections and chest infection under the term "soft tissue infections" (pre-ADEC letter dated 8 November 1993).

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EXTRACT OF RATIFIED MINUTES OF THE 1993/5 (155th) MEETING OF THE AUSTRALIAN DRUG EVALUATION COMMITTEE 2-3 DEC 1993

4.12.14 The clinical evaluator had reported that 79 of 90 patients treated for osteomyelitis for 6 weeks with teicoplanin were cured or improved. The success rate with septic arthritis was 94% after use of a higher dose. The non-pivotal studies did not distinguish between bone and joint infections.

4.12.15 In the pivotal study of bacteraemia and septicaemia, there was a clinical cure rate of 80% using either teicoplanin or vancomycin. It was not clear from the reports of the clinical trials whether teicoplanin had been given by bolus or by slow infusion.

4.12.16 Teicoplanin is said not to cause the "Red Man" syndrome. In the bone and joint infection study, the drug was discontinued in 17% of patients because of a variety of adverse reactions. Overall, of 3377 patients, 347 suffered adverse reactions: 89 with allergy; 57 with altered liver function tests; 27 with pyrexia; 55 with local intolerance, 55 with ototoxicity; and 22 with altered renal function.

It was noted that higher doses of teicoplanin needs are required for severe infections. However, the side effect profile increases with increasing dose. The acceptability of the risk-benefit ratio is questionable. In New Zealand in August 1993, the regulatory authorities deferred acceptance of teicoplanin on the grounds of a lack of resolution of this issue. More evidence of the safety profile at higher doses was requested. A Member noted that for the three indications suggested by the delegate in 'option 2' the standard dose, rather than the higher dose, was recommended, minimizing the risk of toxicity due to using a higher dose.

4.12.17 A Member commented that there may be a role for teicoplanin in situations where vancomycin cannot be used, particularly if the patient develops vancomycin-induced "Red Man" syndrome although there are currently no data to support such use.

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4.12.19 Concern was expressed regarding the possible development of resistance to teicoplanin. XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX. A member therefore suggested that an additional sentence XXXXXX XXX XXXXX XXXX XXX XXX XXXXXX XXXXXX would be appropriate for teicoplanin, ie "As it is the only available antibiotic to which nearly all staphylococci and streptococci remain sensitive, its use should

be reserved to specific indications". The Meeting discussed this proposal and specifically whether the statement should be part of the indications for teicoplanin or occur as a general statement in the Product Information.

The Committee considered that the proposed indication for prophylaxis could not be supported.

4.12.20 In conclusion, a majority of the members agreed to recommend registration and requested that the delegate take into account the ADEC comments when finalising the Product Information with the company. The Meeting resolved to advise the Minister and the Secretary that:

RESOLUTION NO 5306

THE APPLICATION BY MARION MERRELL DOW AUSTRALIA PTY LTD FOR REGISTRATION OF TARGOCID LYOPHILISED POWDER FOR RECONSTITUTION TO PROVIDE A SOLUTION CONTAINING TEICOPLANIN 100 MG/5 ML, 200 MG/10 ML AND 400 MG/20 ML, FOR IV OR IM INJECTION, SHOULD BE APPROVED FOR THE TREATMENT OF THE FOLLOWING 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.

APPROVAL SHOULD BE SUBJECT TO THE MODIFICATION OF THE PRODUCT INFORMATION TO THE SATISFACTION OF THE TGA.

THE APPLICATION TO REGISTER TEICOPLANIN FOR THE TREATMENT OF ENDOCARDITIS, RESPIRATORY INFECTIONS, SKIN AND SKIN STRUCTURE INFECTIONS, URINARY TRACT INFECTIONS AND PERITONITIS ASSOCIATED WITH CHRONIC AMBULATORY PERITONEAL DIALYSIS, TOGETHER WITH THE APPLICATION FOR THE PROPHYLACTIC USE OF TEICOPLANIN IN SURGICAL PATIENTS, SHOULD BE REJECTED ON THE GROUNDS OF LACK OF DEMONSTRATED EFFICACY IN THESE INDICATIONS.

4.12.21 The ADEC further resolved to advise the Minister and the Secretary that:

RESOLUTION NO 5331

THE USE OF THE TERM "SKIN AND SOFT TISSUE INFECTIONS" IS TO BE DISCONTINUED. THE MORE DESCRIPTIVE TERM "SKIN AND SKIN STRUCTURE INFECTIONS" IS TO BE USED IN ITS PLACE.

ITEM 3.14 TEICOPLANIN - TARGOCID - MARION MERRELL DOW AUSTRALIA PTY LTD

The PSC considered an application by Marion Merrell Dow Australia Pty Ltd for registration of Targocid, lyophilised powder for reconstituting a solution containing teicoplanin, 100 mg/5 mL, 200 mg/10 mL and 400 mg/20 mL, for IV or IM injection, for the treatment of gram-positive bacterial infections. Teicoplanin is a tetracyclic glycopeptide antibiotic complex, produced by Actinoplanes teichomyceticus. The complex consists of 5 A-2 components and an A-3 component, which is formed as a degradation product.

A member of the PSC had noted that the evaluator had been concerned over an issue relating to the presence of the A-3 component in the teicoplanin formulation, and had asked for clarification. Pharmaceutical chemistry evaluators informed the PSC that the teicoplanin complex is primarily a mixture of A-2 components which are formed during fermentation, but an A-3 component forms when the A-2 components are purified. The TGA had been concerned that the A-3 component, although qualitatively similar in activity to the A-2 component, was, on a weight for weight basis less active than the A-2 component, and therefore, the presence of the A-3 component may reduce the overall activity of a dose of teicoplanin. The sponsor had been requested to define the process by which the A-3 component was formed and to attempt to control its synthesis. The sponsor had determined that the A-3 component forms by hydrolysis of the acyl group on the side chain of the A-2 component, but found that attempts to remove the water which caused the hydrolysis required conditions which caused an increase in the formation of the A-3 component. The sponsor had suggested that a balance in these manufacturing processes could be reached, and proposed an upper limit for the A-3 component that could be applied for the raw material and the finished product. The proposed upper limit was considered excessive by the TGA, but was finally agreed to on the basis that this limit had been accepted in 27 other countries.

Another member of the PSC had noted that teicoplanin has an optical rotation of 29.1°, but that this did not appear in the product specifications. The member asked if this was normal practice for compounds derived from a natural fermentation process, and wondered whether this property could be controlled, given the route of synthesis. The member was informed that antibiotics derived from a fermentation process are assumed to exist in a single form, and that small changes in composition would not be expected to have a large impact on the optical activity of the compound. The member agreed that specifications regarding optical rotation would normally need to be addressed for synthetic antibiotics.

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RATIFIED RECOMMENDATION OF THE
PHARMACEUTICAL SUBCOMMITTEE OF
AUSTRALIAN DRUG EVALUATION COMMITTEE
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The PSC were satisfied that all matters of chemistry and quality control had been resolved. The PSC were also satisfied with the bioavailability studies, which had found IM and IV administered teicoplanin to be bioequivalent with respect to AUC, although Tmax was increased and Cmax was reduced after IM administration.

The PSC resolved to recommend to ADEC that:

RECOMMENDATION 587

THE PSC RESOLVED THAT THERE SHOULD BE NO OBJECTIONS ON PHARMACEUTICAL CHEMISTRY, QUALITY CONTROL OR BIOAVAILABILITY GROUNDS TO APPROVAL OF THE APPLICATION BY MARION MERRELL DOW AUSTRALIA PTY LTD FOR REGISTRATION OF TARGOCID LYOPHILISED POWDER FOR RECONSTITUTING A SOLUTION CONTAINING TEICOPLANIN, 100 MG/5 ML, 200 MG/10 ML AND 400 MG/20 ML, FOR IV OR IM INJECTION.

THE PSC WAS CONCERNED THAT AN ACTIVE DEGRADATION PRODUCT (COMPONENT A_3) WAS FORMED DURING THE PURIFICATION OF TEICOPLANIN BULK SUBSTANCE, BUT AGREED TO ACCEPT THE FINISHED PRODUCT SPECIFICATIONS FOR THIS COMPOUND ON THE BASIS OF THE SPONSOR'S ARGUMENTS.