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File No: 93/16630
Application No: 91/156/2
Evaluation No: A030

Director
Drug Evaluation Branch
Attention : [redacted]

PART II EVALUATION
APPLICATION FOR REGISTRATION
TEICOPLANIN
'TARGOCID' POWDER FOR INJECTION IN VIALS
100, 200 AND 400 mg PLUS WATER FOR INJECTION
MARION MERRELL DOW AUSTRALIA PTY LTD

The chemistry and quality control evaluation of the above application has been completed except for one issue outstanding relating to revisions to the Bacterial Endotoxins test methods which need not delay the progress of this application to ADEC.

There is no objection to registration of these product containing the antibiotic teicoplanin with respect to chemistry and quality control.

[redacted] has prepared a summary of Part II aspects for ADEC (folios 33-37) and [redacted] has contributed the bioavailability component of the summary. A listing of folios relevant to the ADEC submission is attached (folio 38) to assist the ADEC Secretariat.

The DGAS forms (folios 26-23) are acceptable and consistent with the information provided for evaluation.

Your attention is drawn to several matters concerning the draft Product Information submitted under cover of the company's letter of 12 April 1991. A copy of the draft document is to be found on folios 106-112 (file 86/9010). The evaluator's comments are to be found on the following folios:

File 86/9010	122-121
	190-189 (points 14.3 and 14.6)
	205
File 93/16630	32

Please note in respect of the special reconstitution procedure recommended for the product, the United Kingdom approved product information leaflet (see folio 103 file 86/9010) provides an excellent description of what is required in the section METHOD OF PREPARATION. These instructions would be appropriate for the Australian Product Information.

The Consumer Product Information was not provided for assessment.

[redacted].

[redacted]
Chief Scientist
Antibiotics Section
TGAL
29 September 1993

File No: 93/16630
Application No: 91/156/2
Eval No. A030

Secretary, ADEC
ITEM FOR NEXT ADEC MEETING
APPLICATION FOR REGISTRATION

"TARGOCID"
TEICOPLANIN POWDER FOR INJECTION
10, 200 AND 400mg in colourless glass vials
PLUS WATER FOR INJECTION

MARION MERRELL DOW AUSTRALIA PTY LTD

The following Part II information should be supplied to ADEC.

File No: 86/09010

Folio Nos: 9 -21 (Chem. & Q.C Evaluation Clinical Trial)
135-106 (Chem.& Q.C Evaluation)
142-136 (Questions to the Sponsor)
172 (Evaluation of safety responses)
183-181 (Evaluation of responses to sterility matters)
197-184 (Evaluation of Chem.& Q.C Responses)
203-198 (Further Questions to the Sponsor)
210-204 (External bioavailability evaluation)
226-224 (Evaluation of Responses to sterility matters)
227 (Evaluation of responses to safety matters)
231-228 (Evaluation of Chem. & Q.C Responses)
232-236 (Further questions to the Sponsor)

File No: 93/16630

Folio Nos: 11-12 (Evaluation of responses to safety matters)
13-18 (Evaluation of Chem. & QC Responses)
22-20 (Further questions to the Sponsor)
26-23 (DGAS Information)
33-37 (ADEC Part II summary)

[redacted]
Chief Scientist
Antibiotics Section, TGAL
29 September 1993

File No: 93/16630
formerly (86/9010)
Application No: 91/156/2

ADEC SUMMARY - PART II (CHEMISTRY, QUALITY CONTROL AND BIOAVAILABILITY)

APPLICATION FOR REGISTRATION

TEICOPLANIN "TARGOCID" POWDER FOR INJECTION
100, 200 AND 400mg IN COLOURLESS GLASS VIALS PLUS AMPOULES OF WATER FOR INJECTION
MARION MERRELL DOW AUSTRALIA PTY LTD

CHEMISTRY AND QUALITY CONTROL SUMMARY

"TARGOCID" injection contains the new acylated glycopeptide antibiotic complex teicoplanin (see Appendix 1).

This antibiotic complex derived from fermentation, inhibits the growth of gram positive bacteria by inhibiting the synthesis of bacterial cell wall peptidoglycans. The teicoplanin complex is structurally related to vancomycin and shows similarities in specificities and mode of action.

The five main A_2 components have similar activities on a weight or specific activity basis whereas the degradation product A_3 caused by the loss of the acyl substituent is less active on a weight or specific activity basis.

Teicoplanin injection is intended for use in the treatment of infections caused by gram positive organisms including cases where the organisms is resistant to other antibiotics such as penicillins and cephalosporins or where the patient is allergic to penicillins and cephalosporins.

The raw material and the finished products are manufactured in Italy at the Gruppo Lepetit S.p.A Brindisi plant. The standard of GMP at the raw material and finished product manufacturing /production sites is acceptable.

Three pack sizes have been proposed viz:
100 mg in a 5 mL vial with 1.7 mL water for injection ampoule
200 mg in a 10 mL vial with 3.14 mL water for injection ampoule
400 mg in a 25 mL vial with 3.14 mL water for injection ampoule

The vials are USP Type 1 flint glass and all are sealed with 20 mm halobutyl rubber closures. An aluminium ring is used to seal the rubber stoppered vials.

The formulations for the three proposed dosage presentations have variable overages related to losses sustained in reconstitution and from degradation rates over the proposed shelf life storage

conditions.

Presentation label vial content (mg)	100	200	400
Vial size (mL)	5	10	20
Teicoplanin (sodium)(mg)	125	220	460
overage %	25	10	15
Sodium chloride mg	14.3	24.0	24.8

The shelf life of three years when stored below 25°C has been established.

The composition test (HPLC) measures the relative proportions of components in the teicoplanin complex. The formation of the degradation product A_3 occurs during the isolation and purification of teicoplanin bulk substance. Note that A_3 is not present in the fermentation broth. The rise in A_3 content was of concern as this component has less biological activity than the A_2 and related substance components (specific activity basis). The company's limits of individual components were generous with respect to the proportion of A_3 degradation component allowed in the raw material and the finished product. This was not entirely satisfactory. However, as a compromise the company's proposed limits for this test were accepted in view of the facts that these limits have been accepted in 27 other countries including the UK and the Netherlands and that the A_3 component had biological activity be it reduced when compared with A_2 components.

A number of issues concerning manufacture of the active ingredient, specifications applied to the active ingredient, formulation and manufacture, and finished product specifications were taken up with the sponsor. These issues have been resolved. There is no objection to the registration of 'Targocid' powder for injection with respect to chemistry and quality control.

Bioavailability aspects of the application were considered separately. A summary of the bioavailability component follows.

BIOAVAILABILITY SUMMARY

In support of the registration application for this product, the company provided the results of two bioavailability studies (dated 1984 and 1990) comparing the bioavailability of teicoplanin when administered by IV and IM routes. The 1990 study was evaluated by an external evaluator who noted that the major conclusions of the two studies were very similar.

Details of the 1990 bioavailability study are as follows:

The pharmacokinetics and bioavailability of teicoplanin following

single dose intravenous and intramuscular administration of 6 mg/kg to 23 normal healthy male volunteers were investigated using the 400 mg/3 mL formulation (proposed for registration in Australia).

The external evaluator agreed with the sponsor that teicoplanin given by intramuscular administration could be considered bioequivalent to teicoplanin given by intravenous administration with respect to extent of absorption. However, for the intramuscular administration, there was an increase in Tmax and reduction in Cmax when compared with the intravenous administration. The mean values (± sd) of the estimated pharmacokinetic parameters and 90% confidence intervals of the ratio IM/IV are given below:

Parameter	IM	IV	Ratio (%) IM/IV (90% C.I.)
AUCO-OO (mg/Lxh	644.7±100.4	575.9±86.3	111.9 (107.6-116.3)
T1/2 (h)	198.9±48.7	177.9±40.5	111.2 (102.1-120.3)
Cmax (mg/L)	12.9±5.9	46.3±12.0	note 1
Tmax (h)	4.1±1.2	0.51±0.02	note 1

Note 1: Since Tmax and Cmax after intravenous infusion depend on the rate and duration of the infusion, comparison with results for intramuscular injection was not made.

The mean plasma concentration - time profiles are given in appendix 2

[redacted]

[redacted]

Antibiotics Section
Therapeutic Goods Administration Laboratories

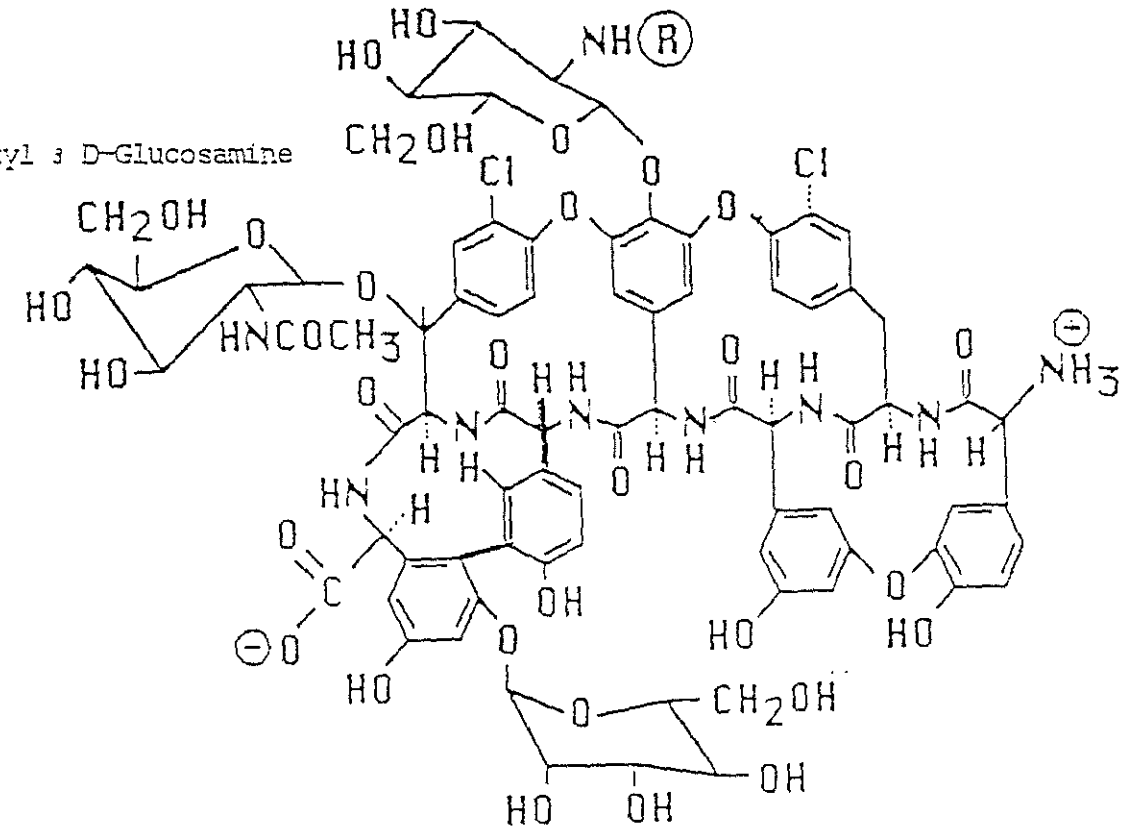
29 September 1993

APPENDIX 1

STRUCTURE OF TEICOPLANIN COMPLEX

N Acyl β D-Glucosamine

N Acetyl β D-Glucosamine



α D-Mannose

Acyl Substituent:

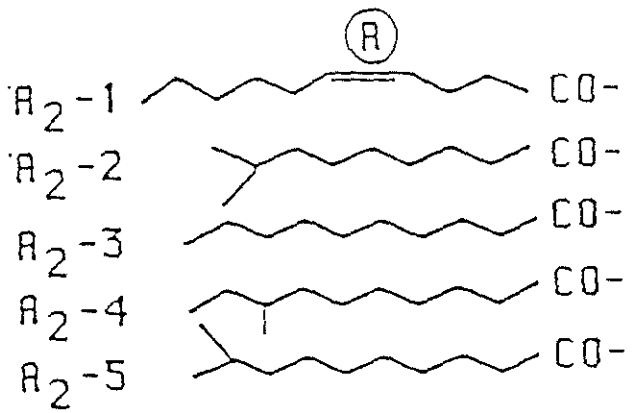


FIGURE1. MEAN TEICOPLANIN SERUM CONCENTRATION TIME PROFILE
FOLLOWING SINGLE DOSE IV AND IM ADMINISTRATION
OF 6 MG/KG (102–018)