File no: 93/16630
Appl. no: 91/156/2
Eval. no: A030

FILE NOTE

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

Correspondence: Company letters of 12 March 1991, 29 July 1991 and 12 September 1992. Company reply of 1 December 1992 to TGA's letter of 25 August 1992. Company reply of 29 April 1993 to TGA's letter of 12 February 1993. Company reply of 29 July 1993 (ff file 93/16630) to TGA's letter of 10 June 1993 (ff 236-234 file 93/16630).

EVALUATION OF COMPANY RESPONSES

7.2 COMPOSITION LIMITS FOR RAW MATERIAL AND FINISHED PRODUCT SPECIFICATIONS

The company contends from the evidence they have provided (letter & attachments 3 & 4, 1 December 1992) that the microbiological activities of the A_3 components were only slightly less in some cases than that of the A_2 complex.

This is a distortion of the data provided. The A_2 and related substances are known to have very similar biological activities; however, the issue in question is what is the activity of the main degradation product A3-1. To make the comparison one must look at the MIC (µg/mL) values quoted from Malabarba et al (1984) Table 8 and Coronelli et al 'Il Farmaco' 42 Table VI. (These published Tables were the only relevant data provided by the company).

MIC values are provided for the teicoplanin complex (which is largely A_2 components) and for the A3-1 component.

I have taken and transformed this published data to compare activities on a molar basis using molecular weights of 1880 for the A_2 components and 1562 for the A3-1 component. The results are presented in APPENDIX 1. Bearing in mind that the teicoplanin complex is a mixture then the comparison of relative activities is a **minimum difference only.**

RESULTS - Only * two organisms of the target group Gram positives viz Staphylococcus aureus Tour Strain (at certain concentrations only) and Staphycococcus epidermidis ATCC 12228 show no difference in biological

activity. For the rest (10 strains quoted and the Tour strain at 10^4 organisms/mL) the A3-1 component is 2.4 to 40 times less inhibitory on a molar basis than the teicoplanin complex (A_2 components).

The conclusions to be drawn are :

1. that the degradation product A3-1 has biological activity albeit on a molar basis of 2 to 40 times less than the A_2 and related substance (RS) components. In vitro susceptibility testing has produced variable results in the literature.

2. - The literature suggests there are less side effects problems and lower toxicity with teicoplanin than with the analogue drug vancomycin (Pharmaceutisch Weekblad 13 (1991) 153-160; Drugs 40 (1990) 449-486; J.Antimicrobial Chemotherapy 22 (1988) 397-399; Med.J.Aust. 156 (1992) 53-57).
   - At this stage I have not seen any reported problems of toxicity etc. due to the degradation product A3-1.

3. The drop in potency of 5 to 8% over the proposed 3 year shelf life when stored below 25°C is concomitant with a loss of 2 to 4% A_2 and a corresponding rise in A_3 components. The test organism for quantitation of the potency of the teicoplanin complex is Bacillus subtilis ATCC 6633. For the teicoplanin assay TGA has used another strain of the same organism- NCTC 8236 equiv. to ATCC 11774).

   It is reiterated again that the company's limits are very generous with respect to A_3 and conservative with respect to A_2 relative contents.

   The batch data provided in earlier correspondence shows that batches would meet more stringent composition limits especially with respect to the finished product with A_2 levels above 80% at expiry and the highest A_3 level being 15.9% after 36 months storage at 25°C. Most batches of raw material manufactured by the current process would meet a higher A_2 limit and lower A_3 limit at release. It should also be noted that the company has the capacity and processes to reprocess 'poor' batches to reduce the A_3 content.

SUMMARY OF COMPANY'S PROPOSED LIMITS

COMPONENT	RAW MATERIAL		FINAL PRODUCT	
	% release	%expiry	%release	%expiry
A_2	NLT 83.0	NLT 80.0%	NLT 78.0	NLT 75.0
A_3	NMT 12.0	NMT 15.0	NMT 17.0	NMT 20.0
R5	NMT 5.0	NMT 5.0	NMT 5.0	NMT 5.0

CONCLUSIONS

The company is reluctant to change the composition limits and states that these limits have been accepted in 27 countries including the UK, the Netherlands.

In view of the albeit reduced biological activity of A3-1 as compared with A_2 components against the target group of gram positive organisms and because of the apparent low toxicity of the A_3 degradation products, I propose that at this time the company's limits be accepted. However, I do feel that the initial A_3 limit for the raw material is high and reflects processing not well controlled. The fermentation broth contains no A_3. This matter may need to be resurrected with the company at a future stage.

ACCEPTABLE AT THIS STAGE

STERILITY MATTERS

12.3 The responses are acceptable (see f10)

ACCEPTABLE

SAFETY MATTERS

The evaluation of safety matters (Questions 13.1, 13.2, 13.3) is found on folios 11-12 this file.
There remain some outstanding matters

TO BE RESOLVED

OTHER MATTERS

1. DGAS FORM.
   The company should be asked to supply the necessary information.

2. PRODUCT INFORMATION LEAFLET
   There are several outstanding matters to be brought to the attention of the MSA for comment. The relevant cross referencing is as follows:

   File 86/09010
   . Folios 103-2 British Product Info Leaflet (contains good description of reconstitution procedure).
   . Folios 112-106 Company's Product Information Leaflet submitted with letter of 12/1991.
   . Folios 122-121, 189, 205 and 215-214 Evaluator's comments for the attention of the MSA concerning the Product Information Leaflet.

RECOMMENDATIONS AND CONCLUSIONS

- There remain some outstanding safety matters

- The company should be asked to provide a Description of Goods for Acceptability to Supply.

These have been dealt with in the accompanying Section 31 letter to the company.

- The concerns regarding the Product Information Leaflet should be brought to the attention of the MSA.

The approval for registration is not recommended until the outstanding matters have been resolved.

[redacted]
Antibiotics Section
TGAL
6 September 1993

APPENDIX 1

Organism	MIC µg/ml Teico Complex	A3-1	Relative Activity by weight complex/A3-1	Specific Activity Teico Complex	NMoles/mL A3-1	Relative Activity Molar Complex/A3-1
Staphycoccus aureus ATCC 6538	0.1	0.4	x4	0.05	0.256	x4.8
Staph. aureus Tour	0.4	0.4	x1	0.213	0.256	x1.2*
at 10^4 org/mL	0.8	1.6	x2	0.425	1.024	x2.4
in BSA	0.4	0.4	x1	0.213	0.256	x1.2*
Staph. epidermidis ATCC 12228	0.4	0.4	x1	0.213	0.256	x1.2
Streptococcus pyrogenes C203	0.05	1.6	x32	0.027	1.024	x38
Strep. pneumoniae UC41	0.05	1.6	x32	0.027	1.024	x38
Strep. faecalis ATCC7080	0.2	1.6	x8	0.106	1.024	x9.7
Staph. aureus	0.125	0.25	x2	0.06	0.160	x2.4
Staph. haemolyticus	4.0	8.0	x2	2.128	5.122	x2.4
Staph. epidermidis	0.125	0.25	x2	0.06	0.160	x2.4

Strep. pyrogenes	0.06	0.5	x8.3	0.032	0.320	x10
Strep. pneumoniae	0.06	0.5	x8.3	0.032	0.320	x10
Strep. faecalis	0.06	2.0	x33.3	0.032	1.280	x40