CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-285

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

Review for Stability Data

NDA#:	21-285 N(BC)
APPLICANT:	Novartis
NAME OF DRUG:	Trileptal® Oral Suspension
DATE OF DOCUMENTS:	July 28, 2000 and February 7, 2001
CHEMISTRY REVIEWER:	Danae Christodoulo, Ph.D. (HFD-120)
STATISTICAL REVIEWER:	Yeh-Fong Chen, Ph.D. (HFD-710)

This review mainly focuses on answering the following two questions raised by the chemistry reviewer:

1. What is the estimated expiration date calculated for Trileptal Oral Suspension based on the TRILEPTAL/DS, Methylparaben, Propylparaben, Sorbic Acid, and Ascorbic Acid content, as well as Total Degradation Products?

2. What is the estimated level of Ascorbic Acid (antioxidant) after 24 and 36 months? Note that ascorbic acid decays via first order kinetics.

I. Background

Novartis submitted its Stability Commitment Report in July of 2000 and provided the updated drug product stability information in February of 2001 with stability data for 4 batches: H8002, H8003, H8004 and H9001. For the first three batches, data were provided for 24 months but for the fourth batch for only 12 months. The shelf life requested by the sponsor was 36 months.

II. Sponsor's Calculated Shelf Lives and Conclusions

1. Content of TRILEPTAL/DS

Storage Condition	Batch	Shelf Life (months)
25°C/60% RH	H8002	57
	H8003	71
	H8004	67
	H9001	72
30°C/70% RH	H8002	51
	H8003	63
	H8004	60
	H9001	64

Based on content of TRILEPTAL/DS, the calculated shelf lives for all conditions lie well above the requested shelf life of 36 months.

2. Content of Ascorbic Acid

Storage condition	Batch	Shelf life [months]
25°C/60% RH	All	61
30°C/70% RH	All	51

Based on content of ascorbic acid, the calculated shelf lives for all conditions lie well above the requested shelf life of 36 months.

3. Conclusions

Four batches of Trileptal® 6 % oral suspension in the market containers were submitted to stability tests under various conditions. Stability data are available for up to 24 months. The stability testing will continue up to the end of the intended shelf life of the product (36 months).

Based on the stability data provided, the sponsor stipulates the following shelf lives, storage instructions, and consumption periods:

Climate	Temperate, Mediterranean subtropical Climate zones I & II	Hot, dry Climate zone III	Hot, humid (tropical) Climate zone IV
Container	**Brown glass bottles with tight closures**	**Brown glass bottles with tight closures**	**Brown glass bottles with tight closures**
Storage Instructions	**None**	**None**	**None**
Shelf life	**36 months**	**36 months**	**36 months**
Consumption Period	**Storage after first opening: 7 weeks at temperatures not above 30°C**	**Same as the previous climate**	**Same as the previous climate**

III. <u>Reviewer's Answers to the Questions</u>

1. Table 1 below shows the estimated shelf lives based on various test parameters under the 25°C/60% RH and 30°C/70% RH conditions (see Appendix I for details). It was noticed that the estimated shelf lives are all greater than 36 months under 25°C/60%

RH but not under 30°C/70% RH. The estimated shelf life for the content of methylparaben and propylparaben show 31 months and 17 months, respectively, under 30°C/70% RH. Therefore, the sponsor's requested shelf life of 36 months is not supported at this condition. At 30°C/70% RH, the shelf life should be 17 months. However, since the estimated shelf life of 17 months is due to the fourth batch, i.e., Batch H9001, which has only 12 months data, it is recommended that the sponsor re-estimate the shelf lives as more data become available.

Table 1: Estimated shelf lives [months]

Test Parameter	25°C/60% RH	30°C/70% RH
TRILEPTAL/DS	72	>200
Methylparaben	118	**31**
Propylparaben	66	**17**
Sorbic acid	141	67
Ascorbic acid (after logarithmic transformation)	72	48
Total Degradation products	>200	>200

Note: Extrapolating the data beyond the actual observed times assumes that the observed pattern of degradation will be maintained in the future.

2. In aqueous solutions, ascorbic acid is known to undergo degradation by oxidation and solvolysis according to first order kinetics. The formula for the first order kinetics is $[A]_t = [A]_0 \exp(-k\ t)$, where [A] denotes the total ascorbic acid concentration and k is the pseudo first order rate constant. Thus, before fitting data by linear regression, the data for the content of ascorbic acid should be logarithmically transformed. Predicted values can be found by taking an exponential transformation from the mean regression line.

   Table 2 below and the graphs in Appendix II show the predicted values and their 95% confidence limits for ascorbic acid up to 40 months under the 25°C/60% RH and 30°C/70% RH conditions. The fitted model for data of ascorbic acid after logarithmic transformation is Model III, i.e. separate slopes and separate intercepts, at 25°C/60% RH, but is Model I, i.e. common slope and common intercept, at 30°C/70% RH. For 25°C/60% RH the predicted values and 95% confidence limits were determined by the fitted regression line of Batch H8004 because these data represent the most conservative situation. For 30°C/70% RH the predicted values are determined by the fitted regression line of the pooled data. The minimum required amount of at least 10% is projected to be reached at some time after 40 months.

Table 2: Predicted Values for Content of Ascorbic Acid from 24 months to 40 months

	25°C/60%			30°C/70%		
	Mean	Lower Limit	Upper Limit	Mean	Lower Limit	Upper Limit
24 months	48.37			32.31		
25 months	46.95			30.86		
26 months	45.58			29.47		
27 months	44.25			28.15		
28 months	42.95			26.89		
29 months	41.70			25.68		
30 months	40.48			24.53		
31 months	39.30			23.43		
32 months	38.15			22.38		
33 months	37.03			21.37		
34 months	35.95			20.41		
35 months	34.90			19.50		
36 months	33.88			18		
37 months	32.89			1		
38 months	31.93					
39 months	30.99					
40 months	30.09					

IV. Additional Comments

1. The sponsor's statistical evaluation for the requested shelf life of 36 months was based on the data of TRILEPTAL/DS and Ascorbic Acid content only. This is not sufficient. This reviewer was asked by the chemistry reviewer to find the estimated shelf life based on the data from several assays and Total Degradation Products.

2. The sponsor performed the stability analyses by combining data of 25°C/60% RH and 30°C/70% RH. This is not appropriate since the drug product can be expected to have substantial different degradation pattern at different storage conditions.

3. This reviewer does not agree with the model used by the sponsor for ascorbic acid stored at 25°C/60% RH. The correct model is Model III, individual regression lines for each batch.

4. The sponsor did not provide the data and stability analysis for substantiating the requested consumption period of 7 weeks.

5. The sponsor also performed long term testing for Trileptal® oral suspension at temperature less than -15°C. This reviewer was told by the chemistry reviewer that it is not necessary to show stability analyses for data at this condition since the sponsor's draft label for marketing in the US has the following storage statement, "Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F)". However,

this reviewer still analyzed the sponsor's data and found the estimated shelf lives (not shown), greater than 36 months for each test parameter that we considered. At this condition it was also noticed that the ascorbic acid content degraded linearly in the original scale.

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Cc: Orig. NDA 21-285
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HFD-120/Ms.Fanari CSO
HFD-700/Dr. Anello
HFD-710/Dr. Chi
HFD-710/Dr. Jin
HFD-710/Ms. Kelly
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This review consists of 5 pages and 3 pages of appendix. MS Word: C:/yfchen/NDA21285/review.doc

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

/s/

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