CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021019

CHEMISTRY REVIEW(S)

M. Mc

SEP 23 1999

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: N 21-019 **CHEM. REVIEW #** 3 **REVIEW DATE:** 9/23/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL*	09/29/97	10/01/97	10/08/97
Amendment	04/30/98	05/04/98	05/10/98
Amendment	11/24/98	11/25/98	11/25/98
Amendment**	**04/27/99**	**04/28/99**	**04/29/99**

* The ORIGINAL submission was as NDA 11-000/S-082/083; subsequently re-assigned this NDA number of 21019. It was not approvable as per Agency letter dated 2/19/98.

****SUBJECT OF THIS REVIEW.**

NAME & ADDRESS OF APPLICANT:

SmithKline Beecham Pharmaceuticals
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19420-0989

DRUG PRODUCT NAME

Proprietary:	Compazine Spansule® Capsules
Nonproprietary/USAN:	prochlorperazine maleate
Code Name/#:	None
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: anxiolytic and anti nausea/vomiting
DOSAGE FORM: [redacted] extended release) capsules
STRENGTHS: 10 mg and 15 mg capsules
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
See USP Dictionary of USAN and International Drug Names, 1996, page 577.

SUPPORTING/RELATED DOCUMENTS:

[redacted]

CONSULTS:
EER: Acceptable 10/98 [redacted]

N21019 (new NDA #) CR#3

REMARKS/COMMENTS:

On April 27, 1999, the applicant submitted an amendment in which provided a complete response to all outstanding issues from the APPROVABLE letter dated March 9, 1999. The applicant's response includes;

> adopting the Agency request to reinstate the previous storage statement, providing sample labels, and a response to the Agency recommended [redacted]

1. The applicant has reinstated the "15° and 30° C" storage statement as described in the 3/9/99 approvable letter.

2. The applicant has provided adequate labeling copy with correct, Description, How Supplied and storage statement information.

3. On page 25 of the 4/27/99, the applicant does NOT propose to adopt the Agency recommended [redacted] specification of [redacted] On page 26 of this amendment, the applicant wishes to retain their originally proposed [redacted] value for this time point. Release data provided for nine batches are also provided on this page. For these nine batches the following [redacted] data apply [all values in percent...93, 89, 90, 86, 84, 87, 86, 91, 87]. The applicant states on page 26, that based on a statistical analysis that there is a [redacted] probability that level-II testing will be necessary. **The applicant is absolutely without a basis for this notion.**

[redacted]

CONCLUSIONS & RECOMMENDATIONS: **From a Chemistry standpoint, it is recommended that this NDA be APPROVED.**

/S/ 9/23/99

Rik Lostritto, Ph.D. Review Chemist

APPEARS THIS WAY
ON ORIGINAL

/S/ 9/23/99

Robert Seevers, Ph.D. Chemistry Team Leader

Init by: _____
filename: C:N21019.r3

APPEARS THIS WAY
ON ORIGINAL

cc:
Org. NDA 21-019
HFD-120/Division File
HFD-120/RLostritto
HFD-120/RSeevers
HFD-120/MMille

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: N 21-019 **CHEM. REVIEW #** 2 **REVIEW DATE:** 02/22/99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL*	09/29/97	10/01/97	10/08/97
Amendment	04/30/98	05/04/98	05/10/98
Amendment	**11/24/98**	**11/25/98**	**11/25/98**

* The ORIGINAL submission was as NDA 11-000/S-082/083; subsequently re-assigned this NDA number of 21019. It was not approvable as per Agency letter dated 2/19/98.

****SUBJECT OF THIS REVIEW.**

NAME & ADDRESS OF APPLICANT:

SmithKline Beecham Pharmaceuticals
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19420-0989

DRUG PRODUCT NAME

Proprietary:	Compazine Spansule® Capsules
Nonproprietary/USAN:	prochlorperazine maleate
Code Name/#:	None
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION: anxiolytic and anti nausea/vomiting
DOSAGE FORM: [redacted] (extended release) capsules
STRENGTHS: 10 mg and 15 mg capsules
ROUTE OF ADMINISTRATION: Oral
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
See USP Dictionary of USAN and International Drug Names, 1996, page 577.

SUPPORTING/RELATED DOCUMENTS:

[redacted]

CONSULTS:
EER: Acceptable. [redacted]

REMARKS/COMMENTS:

The applicant has responded fully and adequately to all chemistry issues.

CONCLUSIONS & RECOMMENDATIONS: From a Chemistry standpoint, it is recommended that this NDA be APPROVED.

/S/ 02/22/95

APPEARS THIS WAY
ON ORIGINAL

Rik Lostritto, Ph.D. Review Chemist

/S/ 2/22/95

Robert Seevers, Ph.D. Chemistry Team LeaderR/D

Init by: _____
filename: C:N21019.r2

DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: N 21-019 **CHEM. REVIEW #** 1 **REVIEW DATE:** 10/25/98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL*	09/29/97	10/01/97	10/08/97
RESPONSE to NA Letter**	04/30/98	05/04/98	05/10/98

* The ORIGINAL submission was as NDA 11-000/S-082/083; subsequently re-assigned this NDA number of 21019. It was not approvable as per Agency letter dated 2/19/98.

****SUBJECT OF THIS REVIEW.**

NAME & ADDRESS OF APPLICANT:

SmithKline Beecham Pharmaceuticals
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19420-0989

DRUG PRODUCT NAME

Proprietary:	Compazine Spansule® Capsules
Nonproprietary/USAN:	prochlorperazine maleate
Code Name/#:	None
Chem.Type/Ther.Class:	3S

PHARMACOL. CATEGORY/INDICATION:	anxiolytic and anti nausea/vomiting
DOSAGE FORM:	(extended release) capsules
STRENGTHS:	10 mg and 15 mg capsules
ROUTE OF ADMINISTRATION:	Oral
DISPENSED:	_X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
See USP Dictionary of USAN and International Drug Names, 1996, page 577.

SUPPORTING/RELATED DOCUMENTS:

CONSULTS:
EER: Acceptable.

[redacted]

CONCLUSIONS & RECOMMENDATIONS: **From a Chemistry standpoint, it is recommended that this NDA is APPROVABLE, pending a satisfactory response to the comments noted herein.**

[redacted]

NOTE: ~~the Biopharm review (dated 10/19/98 recommends a~~ NOT APPROVABLE action). If a resubmission does not contain changes to the composition, process, site of manufacture, test methodology, and/or specifications (other than those cited herein) to the drug product, a 24 month shelf-life should be considered as part of any future

[redacted]

/S/ 10/25/98

Rik Lostritto, Ph.D. Review Chemist

/S/ 10/26/98

Robert Seevers, Ph.D. Chemistry Team LeaderR/D

Init by: _____

filename: C:21019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021019

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21,019 Submission Date: April 27, 1999
Compazine 10 mg and 15 mg Spansule Capsules Smith Kline Beecham
Prochlorperazine Maleate Collegeville, PA 19426
Indication: Nausea and Vomiting Type of Review: Reformulation and Site Change
Reviewer: Raman Baweja, Ph.D. Response to Approvable Letter

The Agency's Approvable letter of March 9, 1999 to the sponsor granted the reformulation of the current 10mg and 15 mg Spansule capsules to their respective new SR capsules

In their response dated April 27, 1999, to the Agency's Approvable letter, the sponsor discusses both the food labelling issue as well as the dissolution specification. Their responses are outlined below with OCPB's responses and Comments:

(1) Effect of Food Labelling Issue: The Agency had sent a Comment to the sponsor that they mention the effect of food on their new SR capsule and this is " Food decreases Cmax by 25 % and AUC by 12 %." The sponsor would like a statement "Food slows absorption of prochlorperazine and decreases Cmax by 25 % but has no effect on AUC."

Comment 1: Both the AUC and Cmax should be mentioned for the effect of food on the new SR capsule and labelling should mention that Cmax decreases by 25 % and AUC by 12 %.

(2) Dissolution: Based on individual unit data submitted on the new 10 mg SR capsule (biobatch, batch no: U97241) and 15 mg new SR capsules (batch no: U96008), the following dissolution method and specification were set
USP Apparatus I (basket) rotated at
900 ml of 0.1 N hydrochloric acid

Specification

The sponsor would like to have the 8 hour specification set The sponsor has sent data from stability batches which show is easily released and that a comparison of each and every one of these batches to the biobatch (U97241)

[redacted]

Comment 2: The following is the dissolution method and specification for the 10 mg and 15 mg new SR Capsules [redacted] that the sponsor should adopt:

USP Apparatus I (basket) rotated at [redacted]
900 ml of 0.1 N hydrochloric acid
Sampling [redacted]

[redacted]

APPEARS THIS WAY
ON ORIGINAL

Recommendation:

The sponsor should mention the effect of food in the labelling for the drug as outlined in Comment 1 above, and adopt the dissolution methodology and specification as outlined in Comment 2 above for both the 10 mg and 15 mg strengths of the SR capsule [redacted]

Please forward this Recommendation and Comments 1-2 to the sponsor.

/S/
Raman Baweja, Ph.D. 8/5/99

RD/FT Initialed by M.Mehta, Ph.D /S/ 8/16/99

cc: NDA 21,019, HFD-120, HFD-860 (Baweja, Mehta), Central Documents Room

APPEARS THIS WAY
ON ORIGINAL

1 page

REDACTED

TRADE Secret/

Confidential

Commercial

FEB 17 1999 COMPLETED FEB - 8 1999

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21,019 Submission Dates: November 24, 1998, Dec. 23, 1998
January 12, 1999

Compazine 10 mg and 15 mg Spansule Capsules Smith Kline Beecham
Prochlorperazine Maleate Collegeville, PA 19426
Indication: Nausea and Vomiting Type of Review: Reformulation and Site Change
Reviewer: Raman Baweja, Ph.D.

Introduction: The 10 mg and 15 mg strengths of Compazine Spansule capsules are approved for nausea and vomiting. The sponsor would like to reformulate the drug product from the current erodible Spansule to a sustained release (SR) capsule where drug release is governed by diffusion. There is a complete change in the excipients of the Spansule capsule particularly noteworthy being the change in the drug release controlling mechanism [redacted] 10 mg capsule [redacted] for the 15 mg capsule. Further, this formulation change is accompanied by a site change where the manufacturing site would change from Philadelphia, PA to Winchester, KY. The new sustained release capsule formulation will, like the current formulation, also be marketed as 10 mg and 15 mg capsules, and, like the current Spansule formulation, the two capsule strengths will differ only in the amount of beads contained in each capsule.

For these formulation and site change issues, the sponsor performed a single dose study using the 10 mg strength at a dose of 30 mg (i.e., 3X10mg capsules) -- A Single Dose Study to Determine the Bioequivalence of Two Sustained Release Formulations of Prochlorperazine Maleate and Compazine Spansules in Healthy Volunteers, (Study Report # 011). Briefly described, this was an open label, randomized, three period, balanced, crossover single dose study involving 48 subjects. The three regimens were: Regimen A which is the current Compazine Spansule - Reference (dose 3X10 mg; batch no: U97272); Regimen B [redacted] (3X10 mg dose; batch no: U97237), and Regimen C [redacted] in both Regimens B and C. Treatments were separated by at least a seven day washout period.

The [redacted] formulation (Regimen C) was shown to be bioequivalent to the current Compazine Spansule capsule.

Mean (SD)	[redacted] SR Formulation	Current Spansule Capsule
AUC(0-inf) (ng*hr/ml)	26.1 (17.0)	30.1 (24.4)

Cmax (ng/ml)	1.28 (0.88)	1.45 (1.1)

The point estimate for AUC(0-inf) for the new 10 mg SR capsule formulation to the current Spansule The 90 % confidence intervals for AUC (0-inf) were 82-94 %.

For Cmax, the point estimate was 0.88 after the administration of the new SR capsules to the current Spansule capsule. The 90 % confidence intervals were 80-98 %

Discussion: OCPB review of October 19, 1998 had conveyed to the firm that the two strengths of Compazine Spansule capsules are undergoing major formulation changes where most importantly the drug release controlling mechanism is totally changing. From a pharmacokinetic standpoint this would involve the characterization of the new Spansule formulation relative to the current one at multiple dosing where the end of dosing interval levels, viz., the Cmins, can be assessed. It is important to ascertain that the levels of the drug produced at the end of the dosing interval from the *new* formulation are equal to, or above that, seen from the current formulation particularly in the absence a clinical study as is the situation in this case. The sponsor was requested to perform a multiple dose study.

The sponsor's submission of November 24, 1998 mentions that their rationale for not performing a multiple dose study is based on safety issues where they had earlier initiated a multiple dose bioequivalency study in healthy subjects for the purpose of transferring the manufacturing site of these capsule from Philadelphia (Study Number: CZ-132). All subjects reported adverse experiences and there were 94 reported adverse experiences; further, eight subjects withdrew from the study with two seeking treatment in an emergency room. Based on this experience the sponsor deemed it inappropriate to expose healthy volunteers to steady state dosing.

The Medical Officer provided us with a clinical perspective that this drug is mostly used on an acute basis for the treatment of nausea and vomiting and is rarely ever used for the manifestation of psychotic disorders which would require multiple administrations. Therefore, steady state performance assessment is not critical clinically.

Simulations: Based on the above viewpoint, the sponsor was requested to perform computer simulations where the single 30 mg dose data for the new SR formulation and for the current Compazine Spansule were used to predict concentrations resulting from multiple dosing (15 mg twice a day for 7 days; q 12 dosing is PDR labelling) based on the principle of superposition.

Q 12 hour Dosing Simulation: The Figure showing the predicted geometric mean and individual C12h values for prochlorperazine following 15 mg twice a day from both treatments, is Attachment II.

Arithmetic mean C12h for the new SR capsule is 1.1 ng/ml (SD 0.7) and that for the current

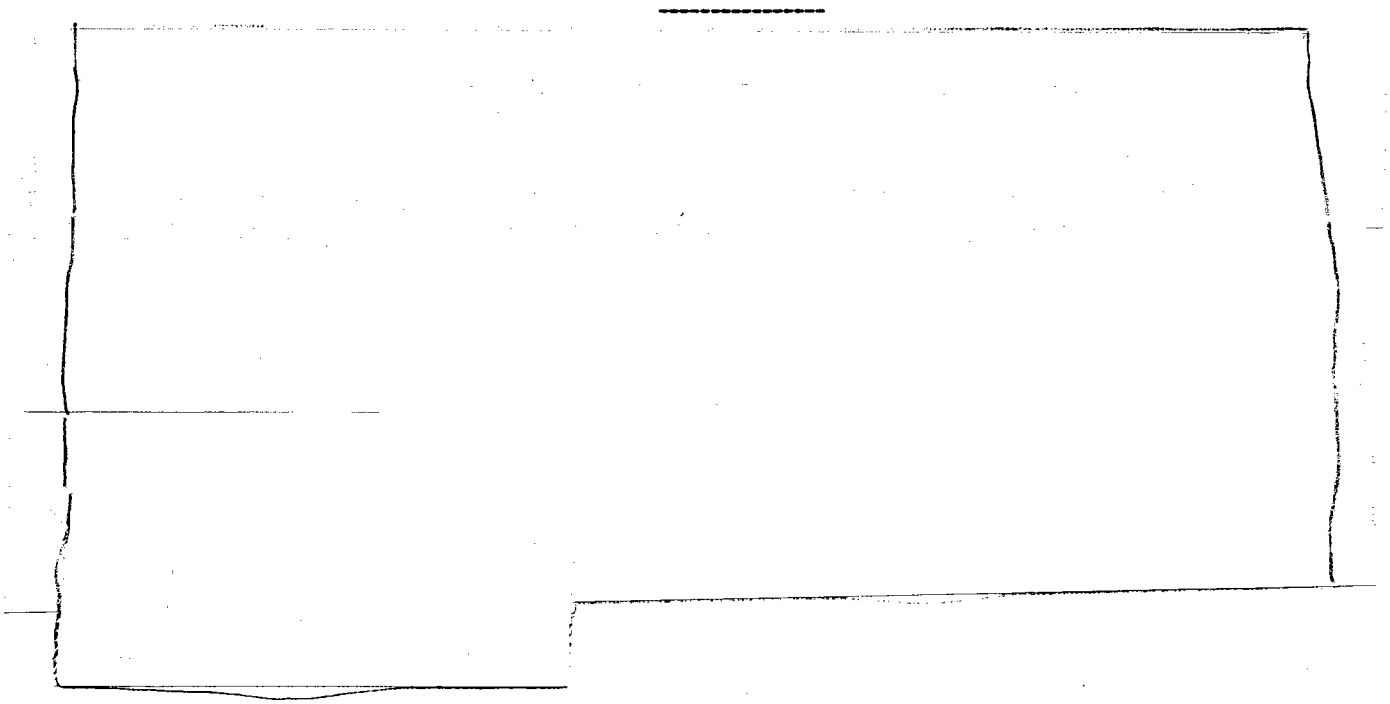
Spansule capsule is 1.3 ng/ml (SD 0.9) -- about 15 % lower for the new SR capsule compared to the current Spansule capsule; these Cmins are essentially around 1 ng/ml. The geometric means are 0.88- and 1.09 ng/ml for new SR and the current capsule, respectively. Finally, the median values were 0.76- and 0.97 ng/ml (new and current capsules).

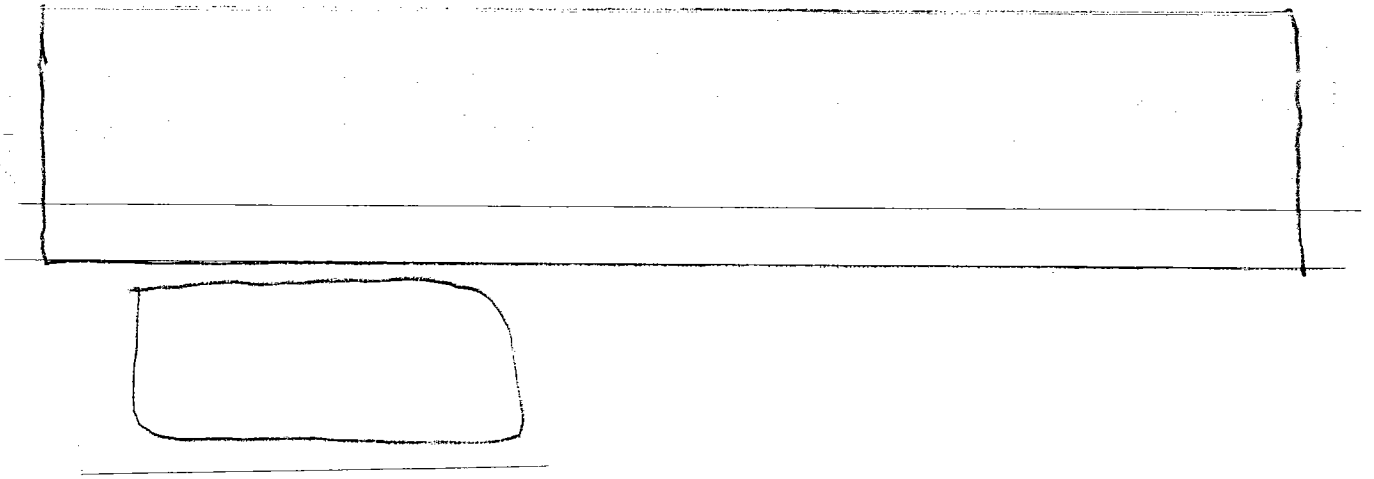
A look at the Figure (Attachment II) also shows that the variability for the new SR capsule is less than that of the current Spansule capsule. The range of individual C12h values for both the formulations is essentially between 0.4-3 ng/ml (Attachment II).
There appear to be two 'outliers' for C12h for current Spansule capsule (values ~ 4.5 and ~5.7 ng/ml). They were identified as subject # 4 and subject #12. (As comparison, their respective C12h values for the new SR capsule were 3.2- and 2.4 ng/ml). It was also noted that for these two subjects their AUC(0-inf) and Cmax values from the current Spansule capsule were higher relative to the new SR capsule in the single dose study - (see below):

Subject 4: current Spansule: AUCinf 111 ng*hr/ml Cmax 4.8 ng/ml
(New SR: AUCinf 82 ng*hr/ml Cmax 2.4 ng/ml)

Subject 12: current Spansule: AUCinf 149 ng*hr/ml Cmax 4.9 ng/ml
(New SR: AUCinf 61 ng*hr/ml Cmax 2.2 ng/ml)

Conclusion: Mean (s.d.) values for C12h from both formulations are comparable. Simulation data suggest that the minimum levels produced at the end of the dosing interval from either formulation are similar and that the new product shows less variability (see also Comment 1).



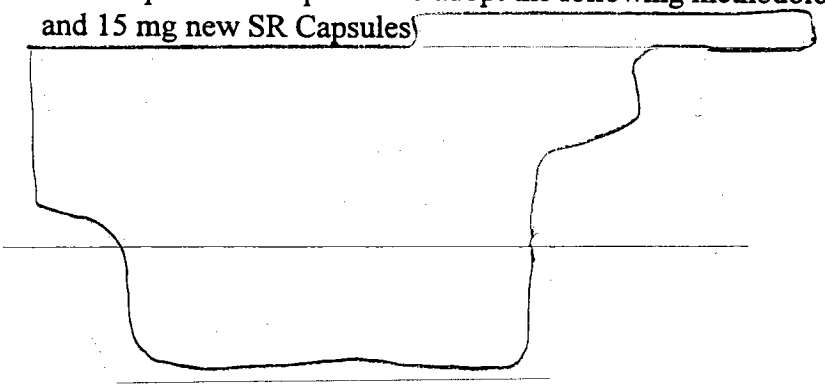


Comments:

1. Simulation data suggest that the minimum levels produced at the end of the dosing interval (C12h) from the new SR formulation are similar to that observed with the current Spansule capsule.

2. In labelling, the sponsor should mention the effect of food on the new SR capsule, viz., Food decreases Cmax by 25 % and AUC by 12 % .

3. The sponsor is requested to adopt the following methodology and specification for the 10 mg and 15 mg new SR Capsules



Recommendation: Reformulation of the current 10mg and 15 mg Spansule capsules to their respective new SR capsules (as well as the site change for manufacturing these new SR Capsules from Philadelphia, PA to Winchester, KY - is granted. The sponsor should mention the effect of food in the labelling for the drug (Comment 2). Finally, they are requested to adopt the dissolution methodology and specification as outlined in Comment 3.

Please forward this Recommendation and Comments 1-3 to the sponsor.

/S/

Raman Baweja, Ph.D. 2/16/99

RD/FT Initialed by M.Mehta, Ph.D /S/ 2/17/99

cc: NDA 21,019, HFD-120, HFD-860 (Baweja, Mehta), Central Documents Room (Barbara Murphy)

APPEARS THIS WAY
ON ORIGINAL

9 Pages
REDACTED
TRADE Secret

COMPLETED OCT 2 0 1998

OCT 1 9 1998

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

/S/ 10/20/98

NDA 11,000 [redacted]
New NDA number 21,019
Compazine 10 mg and 15 mg SR Capsules
Prochlorperazine Maleate
Indication: Nausea and Vomiting
Reviewer: Raman Baweja, Ph.D.

Submission Dates: April 30, 1998
May 18, 1998, August 7, 1998
Smith Kline Beecham
Collegeville, PA 19426
Type of Review: Reformulation and Site Change

The 10 mg and 15 mg strengths of Compazine Spansule capsules are approved for nausea and vomiting. The sponsor would like to reformulate the drug product from the current erodible Spansule to a sustained release (SR) capsule where [redacted] There is a complete change in the excipients of the Spansule capsule particularly noteworthy being the change in the drug release controlling mechanism. As for example, for the 10 mg capsule [redacted] Further, this formulation change is accompanied by a site change where the manufacturing site would change from Philadelphia, PA to Winchester, KY. The new sustained release capsule formulation will, like the current formulation, also be marketed as 10 mg and 15 mg capsules, and, like the current Spansule formulation, the two capsule strengths will differ only in the amount of beads contained in each capsule.

For these formulation and site change issues, the sponsor has performed a single dose study using the 10 mg strength at a dose of 30 mg (i.e., 3X10mg capsules), and they have provided dissolution profile data for both the 10 mg [redacted] and 15 mg capsules.

This review will discuss both - the results specific to the bioequivalence study and dissolution performed for this submission, and, also the comprehensive issues related to the application as a whole where there is a major change in the drug release controlling mechanism for the Spansule capsule.

I. Items Specific to this Submission

A. Bioequivalence Study:

Title: A Single Dose Study to Determine the Bioequivalence of Two Sustained Release Formulations of Prochlorperazine Maleate and Compazine Spansules in Healthy Volunteers, (Study Report # 011)

Brief Description of the Study: Details of the formulations are in Appendix I and the details of the study are in Appendix II. Briefly described, this was an open label, randomized, three period, balanced, crossover single dose study involving 48 subjects. The three regimens were: Regimen A which is the current Compazine Spansule - Reference (dose 3X10 mg; batch no: U97272);

Regimen B identified as the BA-AA formulation is 3X10mg reformulated capsule containing [redacted] 3X10 mg dose; batch no: U97237), and Regimen C identified as the AT-AB formulation which contains [redacted] (3X10mg dose; batch no: U97241). [redacted] in both Regimens B and C [redacted] Treatments were separated by at least a seven day washout period.

Results: Appendix III shows the 90 % confidence intervals for AUC and Cmax performed on log transformed data. The point estimate for both AUC (0-t) and AUC (0-inf) for the new 10 mg SR capsule formulations to the current 10 mg Spansule capsules was 0.87. The average extrapolation (based on the extrapolation obtained for each subject) from AUC (0-t) to obtain AUC (0-inf) was about 12 % for all three treatments.

The 90 % confidence intervals for AUC (0-inf) were 81-93 % for the [redacted] formulation (Regimen B), and 82-94 % for the [redacted] formulation (Regimen C).

For Cmax, the point estimate was 0.88 after the administration of the new SR capsules for both the [redacted] and the [redacted] each compared to the current Spansule capsule. The 90 % confidence intervals were 79.6-97 % for the [redacted] formulation (Regimen B) which is just outside the 80-125 % criteria, and 80-98 % for the [redacted] formulation (Regimen C).

In conclusion, the [redacted] formulation (Regimen C) is shown to be bioequivalent to the current Compazine Spansule capsule; for dissolution testing of this biobatch (U97241) - see below.

B. Dissolution: The sponsor performed dissolution testing on the 10 mg (biobatch, batch no: U97241) and 15 mg new SR capsules (batch no: U96008) under the following conditions:

[redacted]

II. Discussion of the Application:

The two strengths of Compazine Spansule capsules are undergoing major formulation changes where most importantly the drug release controlling mechanism is totally changing. For the 10 mg capsule the change is from [redacted]

A single dose study comparing the current and the new formulations as has been described above, does not provide information on the fluctuation characteristics of the drug from either formulation. Thus, while AUCs and Cmaxs can be compared based on a single dose study, it is unknown as to how the Cmin for the new Spansule formulation will compare to the current one. Cmin assessment can only come from multiple dosing. The idea here is to ascertain that the levels of the drug produced at the end of the dosing interval from the *new* formulation are equal to or above that seen from the current formulation. In the absence of a clinical study as in this case, the way to assess for 'minimum' levels is through the conduct of a multiple dose study comparing the two formulations. In short, the sponsor is requested to conduct a multiple dose study comparing the highest strength of their planned new to be marketed Spansule capsule to the currently marketed Spansule capsule.

Since the new formulation has a totally the sponsor should also perform a food study on the highest strength of their new formulation (i.e., the 15 mg Spansule capsule).

Comments Specific to this Submission:

1. The results of the biostudy indicate that the new 10 mg SR capsule formulation) is bioequivalent to the currently marketed 10 mg Compazine Spansule at a dose of 30 mg. However, the new 10 mg sustained release formulation that contains the is not bioequivalent to the currently marketed 10 mg Compazine Spansule capsule.

Overall Comments:

2. The two strengths of Compazine Spansule capsules are undergoing major formulation changes where most importantly the drug release controlling mechanism is totally changing. From a pharmacokinetic standpoint this would involve the characterization of the new Spansule formulation relative to the current one at multiple dosing where the end of dosing interval levels, viz., the Cmins, can be assessed. It is important to ascertain that the levels of the drug produced at the end of the dosing interval from the *new* formulation are equal to, or above that, seen from the current formulation particularly in the absence a clinical study as is the situation in this case. Thus, the sponsor is requested to conduct a multiple dose study comparing the highest strength of their planned new to be marketed Spansule capsule to the currently marketed Spansule capsule.

3. The sponsor should also conduct a food study on the highest strength of their new Spansule capsule to characterize the effect of food.

[redacted]

Recommendation:

Neither the formulation change nor the site change are granted at this time. The two strengths of Compazine Spansule capsules are undergoing major formulation changes where most importantly the drug release controlling mechanism is totally changing. This would therefore mean complete characterization of the new Spansule formulation involving a multiple dose study as well as a food study (see Overall Comments 2-4 above).

The sponsor is requested to perform a multiple dose study which would provide information on the fluctuation characteristics of the new Spansule capsule in comparison to the current Spansule capsule, and a food study using the highest strength of the proposed new Spansule capsules.

Please forward this Recommendation and Overall Comments 2-4 to the firm.

/S/ 10/19/98

APPEARS THIS WAY
ON ORIGINAL

Raman Baweja, Ph.D.

RD/FT Initialed by M.Mehta, Ph.D. /S/ 10/19/98

APPEARS THIS WAY
ON ORIGINAL

cc: NDAs 11,000 and 21,019, HFD-120, HFD-860 (Baweja, Mehta, Malinowski), Central Documents Room (Barbara Murphy)

13 Pages

TRADE Secret

/Confidential

Commercial