CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-179

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-179 / N-000	**SUBMISSION DATE: 15-SEP-99, 16-JUN-00(BB)**
BRAND NAME:	**Renagel®**
GENERIC NAME:	**Sevelamer HCl 400 and 800mg oral ———**
REVIEWER:	**Robert M. Shore, Pharm.D.**
SPONSOR:	**GelTex Pharmaceuticals, Inc., Waltham, MA**
TYPE OF SUBMISSION:	**Original Application: new dosage form Code: 3S**

TERMS AND ABBREVIATIONS:

DMEDP..... Division of Metabolic and Endocrine Drug Products
ESRD.. ..... End stage renal disease
OCPB.. ..... Office of Clinical Pharmacology and Biopharmaceutics

SYNOPSIS:

This document reviews NDA 21-179/N-000 for Renagel 400 and 800mg ———and contains recommendations for DMEDP. The sponsor has conducted in vitro phosphate binding studies using capsule fiil and ground ———in lieu of an in vivo bioequivalence study. This study has determined that the phosphate binding capacity of the ——— and capsule formulations is similar. However, in discussion with DMEDP there is still a concern over the fact that there are no clinical data in this submission generated with the ——— Whether the ——— actually works as well as the capsule in patients remains a question. It is noted that the sevelamer is insoluble in both aqueous solutions and organic solvents so there is no dissolution method, only disintegration.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-179/N-000 submitted 15-SEP-99 and 16-JUN-00. The overall Human Pharmacokinetic Section is acceptable to OCPB. Labeling discussions have been ongoing with the sponsor and DMEDP. This recommendation and comments (p. 5) should be sent to the sponsor as appropriate.

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BACKGROUND:

Renagel (sevelamer hydrochloride) is crosslinked poly(allylamine), a non-absorbed phosphate-binding polymer which is indicated for the reduction of serum phosphorus in patients with ESRD. Renagel is currently marketed as a capsule formulation containing 403mg sevelamer HCl. The dosage ranges from 1 to 10 capsules per meal. The sponsor has submitted this NDA for compressed 400 and 800mg ——— The 400mg —— is smaller than the currently marketed 403mg capsule and the 800mg—— is similar in size to the currently marketed 403mg capsule. The sponsor feels the —— will lead to improved patient compliance. Since sevelamer is not absorbed an *in vitro* phosphate binding study was conducted by the sponsor in lieu of an in vivo bioequivalence study.

DRUG FORMULATION:

How do the capsule and —— formulations differ?

The blend for the —— and capsule are listed in the table below. The 400 and 800mg —— are quantitatively and qualitatively similar. Sevelamer in the capsule accounts for 93% of the blend while in the —— it is 92% of the blend. The —— contain the same excipients as the capsule but in different quantities.

Comparison of Capsule and —— Blend Compositions (Unit Dose)

BLEND COMPOSITION	RENAGEL® 403 MG CAPSULE	RENAGEL® 400	RENAGEL® 800
Sevelamer hydrochloride			
Water			
Stearic acid			
Colloidal silicon dioxide			
Total weight			

The final —— is film-coated. The finished dosage form specifications are presented in the table below.

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Comparison of Capsule and ——Finished Dosage Forms

	RENAGEL® 403 MG CAPSULE	RENAGEL® 400	RENAGEL® 800
Capsule fill or tablet core			
Capsule shell or coating*			
Total weight			
% sevelamer hydrochloride			
Total volume			

*Capsule shell is a hard gelatin shell, —coating is hydroxypropyl methylcellulose and diacetylated monoglyceride.

The proposed —commercial batch size is —and will be produced at the same site as the capsule (as per personal communication with Martha Carter at Geltex). The pilot batches of —used in the in vitro phosphate binding study were —which is at least 10% of the proposed commercial batch size.

The proposed — will have to meet the same phosphate binding specification as the capsule for batch release. This method involves —
— The specification is —

DISINTEGRATION:

Is there dissolution or disintegration data?

Sevelamer is insoluble in both aqueous solutions and organic solvents so there is no dissolution method. The— will have to meet the same disintegration specification as the capsule, as stated in USP<701>. This specification is —

IN VITRO PHOSPHATE BINDING STUDY :

Does the — formulation bind phosphate in vitro in the same manner as the capsule formulation?

The sponsor conducted an in vitro phosphate binding study using the same media as the approved batch release method for Renagel capsule. The study synopsis is located in the appendix. The kinetic binding data submitted by the sponsor in the NDA did not allow an evaluation of the equilibrium binding of phosphate to sevelamer. However, both the sponsor and this reviewer calculated the Langmuir binding constants (k1 and k2) later in the review process as specified in the Cholestyramine in vitro Bioequivalence Guidance of 1993.

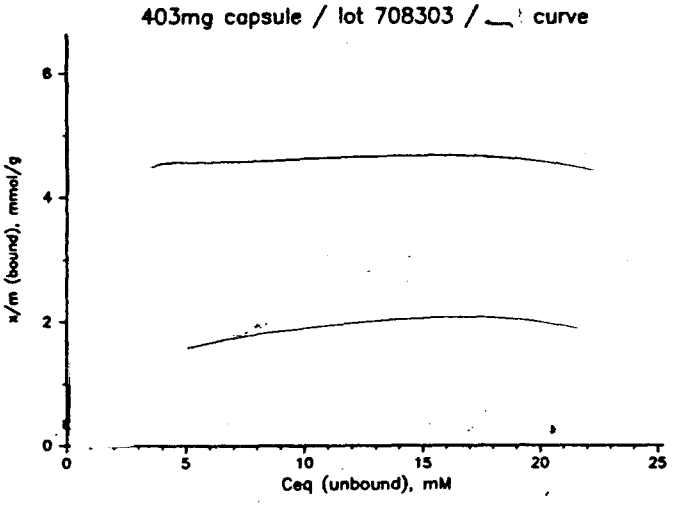
The first set of experiments that the sponsor conducted were done with only three different phosphate concentrations; — Equilibrium binding was assessed at — minutes which is acceptable since binding reached a plateau at about — minutes in all media. Using the three media and the three formulations (403mg capsule, 400 and 800mg —the binding constants were determined using non-linear methods — Although different lots of — and tablets were used in the study, all data for the capsules were combined since this is an approved product and all released lots are acceptable. All data for the 400 and 800mg — were combined since the formulations are identical. Also, combining the limited data allows for a more reliable estimate of the constants. Code and printouts are located in the appendix. The table below summarizes the results.

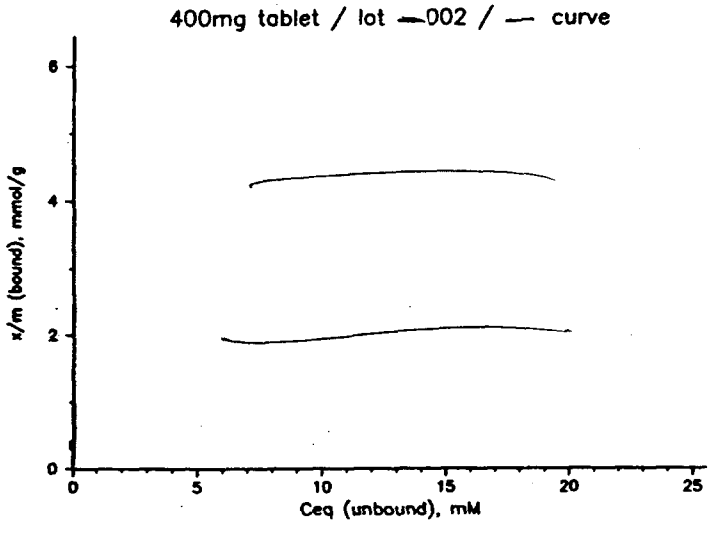
Langmuir constants determined with —media through non-linear methods.

Parameter	403mg Capsule, reference [CV]	——pooled, test [CV]	Ratio, —— Capsule, Test/Ref.
K1 (Affinity)	1.28 [6.4]	1.5 [5.5]	1.15
K2 (Capacity)	6.23 [0.84]	6.0 [0.65]	0.96

As expected, the k1 constant is highly variable but does fall within an acceptable ±20% test-to-reference ratio. The k2 constant is usually more predictable and thus a more strict statistical criteria is placed on it. The 90% confidence interval for the very limited k2 data is 0.94-0.98, calculated with three sets of reference (capsule) data and four sets of test ——, data. The 90%CI falls within the 80-125% bioequivalence limits. The statistical method used was Fieller's Theorem.

On 16-JUN-00 the sponsor submitted results of a similar experiment using —lot of capsules and —lot of 400mg —— This experiment used 8 different media ranging from —— instead of just 3 media. The binding data are presented in the following two plots.





These resulting k1 and k2 constants are summarized in the table below.

Langmuir constants determined with — media through non-linear methods.

Parameter	403mg Capsule, reference [CV]	400mg —— test [CV]	Ratio —— /Capsule, Test/Ref.
K1 (Affinity)	1.14 [6.0]	1.1 [3.8]	0.97
K2 (Capacity)	6.23 [1.6]	6.1 [1.1]	0.97

With more data in this experiment the k1 for the —— formulation seems to be more similar to the k1 for the capsules. The k2 constant is also acceptable.

Taken together, the — media results support the conclusion that the formulations of the capsule and —— bind phosphate in a similar manner.

DISCUSSION:

The data submitted, although not optimal, allow for an evaluation of the binding capacity of the proposed — formulation of Renagel. The system used to evaluate the in vitro phosphate binding of the —— is the same as used for batch release of the approved capsule. The results of the in vitro study in the current NDA indicate that the —— formulation of Renagel binds phosphate to a similar extent as the approved capsule formulation.

The sponsor has stated in Vol 1.5, page 3 that 'For all future in vitro equivalence experiments needed to support manufacturing changes GelTex will use the ——— phosphate ——— BES, and ——— ——— solution because we feel this gives the most discrimination between lots.' They propose to evaluate the changes through a kinetic binding study. However, in order to generate k1 and k2 constants, which is the basis for evaluating in vitro binding for this drug, an equilibrium experiment is needed. This involves various media of different phosphate concentrations. A comment indicating this will be sent to the sponsor.

COMMENTS FROM THE MEDICAL OFFICER:

1) The medical officer is concerned that no data have been submitted to demonstrate that the —— works clinically. The in vitro study demonstrated that the formulations bind phosphate similarly but this study is done with a composite of ——— ——— not the finished dosage form.

COMMENTS TO BE SENT TO SPONSOR:

1) If the sponsor needs to evaluate the in vitro phosphate binding capacity of future formulations of sevelamer, the data submitted will need to be more comprehensive. For example, only three different concentrations of test media were used in this NDA — different test media will be needed in replicate. Also, the sponsor will need to evaluate the equilibrium binding as the primary outcome rather then the kinetic binding. Calculation of k1 and k2 (Langmuir binding constants) is needed. It is advantageous to submit protocols before any study begins.

LABELING COMMENTS:

1) The sponsor needs to include in the labeling (preferably in the Pharmacokinetics section) the following statement:

In vitro studies have shown that the capsule and —— formulations bind phosphate to a similar extent.

Robert M. Shore, Pharm.D. [/S/] 05-JUL-00
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 05-JUL-00

FT initialed by Hae-Young Ahn, Ph.D., Team Leader [/S/] 7/5/00

CC: NDA 21-179/N-000 (orig.,1 copy), HFD-510(Hedin), HFD-870(Ahn, HuangS), HFD-850(Lesko) CDR.

DFS Code: AE

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Appendix 1. Draft labeling

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7 page(s) of revised draft labeling has been redacted from this portion of the review.

Appendix 2. Study summaries

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2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Appendix 3. ADAPT codes and printouts

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10 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.