

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Application Number** 21-160

**APPROVAL LETTER**



NDA 21-160

Braintree Laboratories, Inc,  
Attention: Mark Cleveland, Ph.D.  
Vice President, New Product Development  
60 Columbia Street  
P.O. Box 850929  
Braintree, MA 02185-0929

Dear Dr. Cleveland:

Please refer to your new drug application (NDA) dated September 29, 2000, received October 3, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PhosLo (calcium acetate) Capsules, 667mg and 333.3 mg, and PhosLo (calcium acetate) Gelcaps, 667 mg.

We acknowledge receipt of your submissions dated February 13, March 16, 20, 22, and 29, 2001. Your submission of September 29, 2000, constituted a complete response to our April 4, 2000, action letter.

This new drug application provides for the use of PhosLo (calcium acetate) Capsules and Gelcaps for the control of hyperphosphatemia in end stage renal failure and does not promote aluminum absorption.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 29, 2001, immediate container and carton labels submitted June 3, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-160." Approval of this submission by FDA is not required before the labeling is used.

Sufficient stability data has been submitted to support a 2 year expiry period.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until April 30, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*{See appended electronic signature page}*

David G. Orloff, M.D.  
Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

The labeling submitted on March 29, 2001 is adequate.

Name	Discipline	Signature	Date	Action Recommended
E. Colman	Medical Officer/Team Leader			
K. Davis-Bruno	Team Leader			
S. Markofsky	Chemist			
D. Wu	Team Leader			
R. Shore	Biopharmacy			
H. Ahn	Team Leader			
K. Johnson	SCSO			
D. Orloff	Division Director			

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APR - 4 2000

Braintree Laboratories, Inc,  
Attention: Mark Cleveland  
Vice President, New Product Development  
60 Columbia Street  
P.O. Box 850929  
Braintree, MA 02185-0929

Dear Mr. Cleveland:

Please refer to your new drug application (NDA) dated June 3, 1999, received June 4, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for PhosLo (calcium acetate) Capsules, 667 mg and 333.5 mg, and PhosLo (calcium acetate) Gelcaps, 667 mg.

We acknowledge receipt of your submissions dated June 14, July 27, August 27, and December 22, 1999; and January 6 and 24, and March 8, 2000.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. Please provide a batch size range for the blending phase of the manufacture of PhosLo capsules and gelcaps.
2. The section on " " (Vol. 2.1, pages 10-11), prior to the production of the blend for the gelcaps, is not mentioned in Vol. 1.1, pages 007-014 for the production of the blend for PhosLo capsules. Please explain this discrepancy.
3. The Process-Control range for the yield of the total weight of caplets/batch is listed as  of the actual weight of blend, as shown in step 6.14 (Vol. 2.1, page 20). Please explain how the weight of the caplets obtained can be as much as 10% greater than the weight of the material delivered to the press.

4. The method for the determination of calcium by \_\_\_\_\_ (to monitor the dissolution of the capsules or gelcaps) essentially follows the USP monograph for calcium acetate tablets; but the tablets do not contain gelatin. Provide evidence to show that the gelatin from the capsules or gelcaps does not affect the analysis for calcium.
5. Provide executed Certificates of Analysis (COAs) for a typical batch of both PhosLo half-sized capsules and PhosLo gelcaps.
6. Provide a more specific identification test (e.g. IR) as part of your acceptance criteria for your HDPE bottles.
7. Satisfactory COAs, showing that the relevant items meet their specifications should be part of the acceptance criteria for your packaging components (bottles, \_\_\_\_\_, and liners).
8. Information relating to \_\_\_\_\_ is shown on page 063 of Vol. 2.1. Indicate which of these three HDPE resins will be employed for your 300 and 500 cc containers for PhosLo gelcaps and half-sized capsules.
9. Provide Letters of Authorization (LOAs) so that the Agency can examine \_\_\_\_\_.
10. If there is a code name or code number for the \_\_\_\_\_, your 500-cc bottle, then provide this information to the NDA.
11. Provide specific identification tests (e.g., IR) as part of your acceptance criteria for your F-217, PS-22, and \_\_\_\_\_.
12. We consider that the capsules and caplets are equivalent based on an in vitro dissolution study, and an in vitro phosphate binding study. However, the new caplets cannot be considered equivalent to the tablets at this time. In order to support approval for the caplets, acceptable dissolution tests using 12 dosage units should be conducted in 5 different dissolution media with paddle speed of 50 rpm.

The following dissolution method and specification for the capsules are recommended:

- USP Apparatus I (baskets) at 100 RPM
- 900 mL water
- Specification of not less than  $\frac{Q}{100}$  in 15 minutes.

13. The labeling for NDA 19-976 describes the product as "PhosLo (Calcium Acetate Tablets)". If Braintree Laboratories wishes to retain the name "PhosLo" for all three dosage forms, you may label the products as follows"

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- PhosLo Capsules  
(Calcium Acetate)
- PhosLo Gelcaps  
(Calcium Acetate)

In this scenario both this NDA and NDA 19-976 should be amended to make the name change for labels and all sections of the package insert; and reference to the  $\frac{Q}{100}$ s in the "How Supplied" sections for PhosLo capsules and PhosLo gelcaps should be eliminated.

Also, revisions of the draft labeling submitted on June 3, 1999, may be required after we have reviewed the additional material. Further, we recommend that you withdraw the Regulatory Specifications for "Contents" (the number of capsules or gelcaps/bottle).

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In

the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301) 827-6392.

Sincerely,

*ISI* *4/4/00*  
John K. Jenkins, M.D.  
Acting Director  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

*RH 4/4/00*

cc:  
Archival NDA 21-160  
HFD-510/Div. Files  
HFD-510/R.Hedin  
HFD-510/Reviewers and Team Leaders  
HFD-002/ORM  
HFD-102/ADRA  
HFD-40/DDMAC (with labeling)  
HFD-820/DNDC Division Director  
DISTRICT OFFICE

Drafted by: RH/December 9, 1999

Initialed by: EGalliers/3.30/LLutwak/EColman/SMarkofsky/DWu/HAhn/3.31.00

Final: RHedin/4.1.00

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