CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-160

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 21-160 / N-000	**SUBMISSION DATE:**	**29-SEP-00 (AZ)**
BRAND NAME:	**PhosLo®**	
GENERIC NAME:	**Calcium acetate oral capsules (333.5mg & 667mg) and gelcaps (667mg)**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Braintree Laboratories, Inc., Braintree, MA**	
TYPE OF SUBMISSION:	**Amendment to NDA**	

SYNOPSIS:

PhosLo® tablets are approved for the control of hyperphosphatemia in end stage renal disease. The sponsor submitted a supplement to NDA 19-976 (which became unbundled as NDA 21-160) for dosage form changes from a round tablet to I) capsule dosage forms, full size and half size, and II) a caplet dosage form, which is an elongated calcium acetate tablet inserted into a gelatin capsule. In the review of NDA 21-160/N-000 (submissions dated 03-JUN-99 and 27-AUG-99) Dr. Ahn found that the new capsule formulations were equivalent to the tablet but that additional dissolution data were needed to support the approval of the caplet. This amendment contains these additional dissolution data.

As per Dr. Ahn's review, comparative dissolution data for the caplet and tablet were submitted but these data were generated with Apparatus II (paddles) at **100rpm**. Although all other conditions were acceptable, the sponsor was asked to generate dissolution data in the same 5 media using a paddle speed of **50rpm**.

These data are presented in the table below. The values in the table are averages of 12 dosage units. No unit had a dissolution [redacted] at 15 minutes (see Appendix). Five different media were used as per Dr Ahn's request: water, 0.1N HCl, pH 4.5 buffer, pH 6.8 buffer, and pH 7.5 buffer. The caplet formulation demonstrates comparable dissolution to the approved tablet formulation.

APPEARS THIS WAY
ON ORIGINAL

Media & Product	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
Purified Water:	
Phoslo 667mg Gelcaps Lot P0G160RD	
Phoslo 667mg Tablets Production Lot P0G140	
[redacted]	
0.1N HCL:	
Phoslo 667mg Gelcaps Lot P0G160RD	
Phoslo 667mg Tablets Production Lot P0G140	
[redacted]	
PH 4.5 Acetate Buffer:	
Phoslo 667mg Gelcaps Lot P0G160RD	
Phoslo 667mg Tablets Production Lot P0G140	
[redacted]	
PH 7.5 Borate Buffer:	
Phoslo 667mg Gelcaps Lot P0G160RD	
Phoslo 667mg Tablets Production Lot P0G140	
[redacted]	
PH 6.8 Borate Buffer:	
Phoslo 667mg Gelcaps Lot P0G160RD	
Phoslo 667mg Tablets Production Lot P0G140	

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 21-160/N-000 submitted 29-SEP-00 (AZ). The data is acceptable to support the approval of the caplet formulation of PhosLo®. This recommendation and comments should be conveyed to the sponsor.

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader_____

FT initialed by Hae-Young Ahn, Ph.D., Team Leader_____

CC: NDA 21-160/N-000 (orig.,1 copy), HFD-510(Hedin, Markofsky), HFD-870(Ahn), CDR.

Code: AP

Appendix, Individual dissolution data.

APPEARS THIS WAY
ON ORIGINAL

PHOSLO 667mg GELCAP DISSOLUTION VERSUS 667mg TABLETS

Phoslo 667mg Gelcaps R & D lot P0G160RD Purified Water, ***paddles at 50 rpm***, SG/057/115, 8-4-00	
Gelcap #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	94.0
Range	

Phoslo 667mg Tablets production lot P0G140 Purified Water, ***paddles at 50 rpm***, SG/057/114, 8-4-00	
Tablet #	% of Label Claim of Calcium Acetate *Dissolved in 15 minutes*
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	99.1
Range	

PHOSLO 667mg GELCAP DISSOLUTION VERSUS 667mg TABLETS

Phoslo 667mg Gelcaps R & D lot P0G160RD 0.1N HCL, *paddles at 50 rpm*, SG/057/119, 8-11-00	
Gelcap #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	97.3
Range	

Phoslo 667mg Tablets production lot P0G140 0.1N HCL, *paddles at 50 rpm*, SG/057/119, 8-11-00	
Tablet #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	100.7
Range	

PHOSLO 667mg GELCAP DISSOLUTION VERSUS 667mg TABLETS

Phoslo 667mg Gelcaps R & D lot P0G160RD 0.05M Acetate Buffer pH 4.5, *paddles at 50 rpm*, SG/057/118, 8-10-00	
Gelcap #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	96.4
Range	

Phoslo 667mg Tablets production lot P0G140 0.05M Acetate Buffer pH 4.5, *paddles at 50 rpm*, SG/057/118, 8-10-00	
Tablet #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	99.8
Range	

PHOSLO 667mg GELCAP DISSOLUTION VERSUS 667mg TABLETS

Phoslo 667mg Gelcaps R & D lot P0G160RD 0.05M Borate Buffer pH 7.5, *paddles at 50 rpm*, SG/057/116, 8-7-00	
Gelcap #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
	[redacted]
Average	98.3
Range	[redacted]

Phoslo 667mg Tablets production lot P0G140 0.05M Borate Buffer pH 7.5, *paddles at 50 rpm*, SG/057/116, 8-7-00	
Tablet #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	[redacted]
2	[redacted]
3	[redacted]
4	[redacted]
5	[redacted]
6	[redacted]
7	[redacted]
8	[redacted]
9	[redacted]
10	[redacted]
11	[redacted]
12	[redacted]
	[redacted]
Average	101.3
Range	[redacted]

PHOSLO 667mg GELCAP DISSOLUTION VERSUS 667mg TABLETS

Phoslo 667mg Gelcaps R & D lot P0G160RD 0.05M Borate Buffer pH 6.8, *paddles at 50 rpm*, SG/057/117, 8-9-00	
Gelcap #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	98.0
Range	

Phoslo 667mg Tablets production lot P0G140 0.05M Borate Buffer pH 6.8, *paddles at 50 rpm*, SG/057/117, 8-9-00	
Tablet #	% of Label Claim of Calcium Acetate Dissolved in 15 minutes
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
Average	99.2
Range	

Robert Shore
3/1/01 11:15:49 AM
BIOPHARMACEUTICS
dissolution data acceptable for caplet.
hardcopy S/O on 28-FEB-01

Hae-Young Ahn
3/1/01 12:03:21 PM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-160
PhosLo® Capsules, 667 mg, 333.5 mg
PhosLo® Gelcaps, 667 mg
(Calcium Acetate)

SUBMISSION DATES: 6/3/99
8/27/99

Braintree Laboratories

REVIEWER: Hae-Young Ahn, Ph.D.

SUBMISSION TYPE: Original NDA for New Dosage Forms

SYNOPSIS: PhosLo® tablets are approved for the control of hyperphosphatemia in end stage renal disease. (Note: Patients with advanced renal insufficiency exhibit phosphate retention and some degree of hyperphosphatemia..) The recommended initial dose of PhosLo® for the adult dialysis patient is 2 tablets with each meal. The dosage may be increased gradually to bring serum phosphate value below 6 mg/dl, as long as hypercalcemia does not develop. Most patients require 3-4 tablets with each meal.

The sponsor submitted a supplemental NDA for dosage form changes from a round tablet to I) capsule dosage forms, full size and half size, and II) a caplet dosage form, which is an elongated calcium acetate tablet inserted into a gelatin capsule. The sponsor's submission was unbundled from their approved NDA (NDA 19-976) according to the CDER guidance ('bundling policy') and became an original NDA.

Since the therapeutic action of PhosLo® is to bind phosphate within the lumen of the GI tract to form insoluble calcium phosphate, the sponsor has conducted comparative dissolution tests in 5 different media as well as in vitro phosphate binding studies in lieu of bioequivalence studies.

The capsules, full size and half size, can be considered equivalent to the tablets based on comparative dissolution tests as well as in vitro phosphate binding tests. On the other hand, for the caplets the sponsor conducted comparative dissolution tests with USP Apparatus II (paddles) at 100 rpm, which is not considered as a mild dissolution condition and does not have discriminating capability. Consequently, the caplets can not be considered equivalent to the tablets.

COMMENT:
Dissolution tests for the caplets using 12 dosage units should be repeated in 5 different dissolution media with paddle speed of 50 rpm. This comment was conveyed to the sponsor via fax on 8/20/99 and during a telephone conversation on 3/6/00. The test results have not been submitted yet.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE II) considers that the capsules and PhosLo® tablets are equivalent based on an in vitro dissolution study and an in vitro phosphate binding study. However, the new caplets can not be considered equivalent to PhosLo® 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 of water
Specification of [redacted] in 15 minutes.

This recommendation should be conveyed to the sponsor as appropriate.

Hae-Young Ahn, Ph.D., DPE II, PCPB /S/ 3/14/00

FT initialed by J. Hunt, Deputy Director /S/ 3/14/00

CC: NDA 21-160, HFD-510 (Hedin), HFD-850 (Lesko), HFD-870 (Huang, Ahn, Hunt), CDR

Code: AE

APPEARS THIS WAY
ON ORIGINAL

Dissolution media & Product	% of Label claim of calcium acetate dissolved in 15 minutes
Purified Water:	
Phoslo full size Capsules lot P8G214RD	]
Phoslo half size Capsules lot P8G213RD	]
Phoslo Tablets production lot P8C107	]
0.1N HCL:	
Phoslo full size Capsules lot P8G214RD	]
Phoslo Tablets production lot P8C107	]
Acetate Buffer:	
Phoslo full size Capsules lot P8G214RD	
Phoslo Tablets production lot P8C107	]
pH 7.5 Borate Buffer:	
Phoslo full size Capsules lot P8G214RD	]
Phoslo Tablets production lot P8C107	
pH 6.8 Borate Buffer:	
Phoslo full size Capsules lot P8G214RD	
Phoslo Tablets production lot P8C107	]

Results:

- Both the capsules and tablets are
- Both the capsules and tablets dissolution is essentially the same in any of the 5 dissolution media.
- Dissolution of the capsules and the tablets can be considered equivalent.

Phosphate Binding Study

Since the therapeutic action of PhosLo® is to bind phosphate within the lumen of the GI tract to form insoluble calcium phosphate, a study was set up to compare the products in their capacity to bind phosphate. The binding study was based on an in vitro reaction of a 1:1 mole ratio of calcium in the drug product to a prepared phosphate solution, followed by assay of unbound phosphate.

Sample	Absorbance at 400 nm
Blank	0.000
Standards:	
1/500	
1/100	
3/100	
10/100	(r = 0.99998)
PhosLo Tablets #1	

PhosLo Tablets #2
PhosLo Tablets #3 — Average of 3 = 0.889

PhosLo Capsules #1
PhosLo Capsules #2
PhosLo Capsules #3 — Average of 3 = 0.903

The absorbances of the standard solution are shown to be linear. The PhosLo tablets and capsules have essentially the same absorbance and this indicates that PhosLo tablets and capsules bind phosphate to the same degree.

The proposed initial dose of PhosLo full size capsules for the adult dialysis patient is 2 capsules with each meal and the proposed initial dose of PhosLo half size capsules for the adult dialysis patient is 4 capsules with each meal.

Caplet dosage form:

Q. Can the caplet dosage form be considered equivalent to the tablets?

May be.
The sponsor conducted comparative dissolution tests with USP Apparatus II (paddles) at 100 rpm, which is not considered as a mild dissolution condition. (Note: Guidance for Industry: Dissolution testing of immediate release solid oral dosage forms states the following:

> *"The mean T50% gastric residence (emptying) time is 15-20 minutes under fasting conditions. Based on this information, a conservative conclusion is that a drug product undergoing — dissolution in 15 minutes under mild dissolution test conditions in 0.1 N HCl behaves like a solution and generally should not have any bioavailability problems. If the dissolution is slower than gastric emptying, a dissolution profile with multiple time points in multimedia is recommended..... **Dissolution testing should be carried out under mild test conditions, basket method at 50/100 rpm or paddle method at 50/75 rpm, at 15 minute interval, to generate a dissolution profile.")***

An in vitro phosphate binding study suggests that the PhosLo tablets and caplets have essentially the same absorbance, which indicates that PhosLo tablets and caplets bind phosphate to the same degree.

Formulations:
The sponsor states that the elongated dosage form has the exact same formulation and weight of calcium acetate as the original PhosLo® tablet.

BACKGROUND:
PhosLo® was approved by the Agency as white round tablets.

> *In the original NDA submission, no bioavailability/pharmacokinetic studies were submitted. At that time, the Pharmacokinetic Evaluation Branch (currently the Office of Clinical Pharmacology and Biopharmaceutics, OCPB) granted a bio-waiver based on 21CFR 320.22(b)(3) since the only action of the product is within the GI tract for binding with phosphorus primarily from dietary sources. The following dissolution method and specification were approved:*
>
> *USP Apparatus II (paddle) at 50 RPM*
> *900 ml of water*
> *specification of* ——— *in 15 minutes.*

Unfortunately, OCPB's recommendation on the dissolution method and specification was not conveyed to the sponsor upon approval. The sponsor has been using the dissolution method with **USP apparatus II (paddle) at 100 rpm** with the specification of ~~—~~ t' —— Q) in 15 minutes.

SUBMISSION:

Capsule dosage forms, full size and half size:

Q. Can the capsule dosage forms be considered equivalent to the tablets?

Yes.
Full size capsules can be considered equivalent to the tablets based on comparative dissolution tests as well as in vitro phosphate binding tests. Half size capsules are compositionally proportional to full size capsules and dissolve ~~———~~ in 15 minutes.

Composition:

Full Size Capsule		Half Size Capsule	
Calcium Acetate, USP	mg	Calcium Acetate, USP	mg
Polyethylene Glycol 8000, NF	ng	Polyethylene Glycol 8000, NF	g
Mineral Oil, Light, NF	g	Mineral Oil, Light, NF	g

Dissolution:
The sponsor conducted comparative dissolution tests under the following conditions: water, 0.1N HCl, pH 4.5 acetate buffer and pH 7.5 and pH 6.8 borate buffer, using USP Apparatus I (baskets) at 100 rpm.

Dissolution:

The sponsor conducted comparative dissolution tests under the following conditions: water, 0.1N HCl, pH 4.5 acetate buffer and pH7.5 and pH 6.8 borate buffer, using USP Apparatus II (paddles) at 100 rpm. Proposed caplets release specification is [redacted] in 15 minutes.

Dissolution media & Product	% of Label claim of calcium acetate dissolved in 15 minutes
Purified Water:	
Phoslo full size Caplets lot P8G211RD	[redacted]
Phoslo Tablets production lot P8C107	[redacted]
0.1N HCL:	
Phoslo full size Caplets lot P8G211RD	
Phoslo Tablets production lot P8C107	[redacted]
Acetate Buffer:	
Phoslo full size Caplets lot P8G211RD	
Phoslo Tablets production lot P8C107	[redacted]
pH 7.5 Borate Buffer:	
Phoslo full size Caplets lot P8G211RD	
Phoslo Tablets production lot P8C107	
pH 6.8 Borate Buffer:	
Phoslo full size Caplets lot P8G211RD	
Phoslo Tablets production lot P8C107	[redacted]

Results:

The dissolution study should be repeated, using USP Apparatus II (paddle) at 50 RPM.

Draft Guidance for Industry: Waiver of in vivo bioavailability and bioequivalence studies for immediate release solid oral dosage forms containing certain active moieties/active ingredients based on a biopharmaceutics classification system states the following:

*"An IR drug product is considered rapidly dissolving when not less than 85% of the label amount of the drug substance dissolves within 30 minutes using the USP apparatus I at 100 rpm (or **apparatus II at 50 rpm**) in a volume of 900 ml, or less in each of the following media.....For waiver of bioeqivalence, test and reference products should exhibit similar dissolution profiles under the dissolution test conditions defined for rapidly dissolving products. ....When both the test and the reference products dissolve 85% or more of the label amount in < 15 minutes, in all three dissolution media recommended above, a profile comparison is unnecessary."*

Phosphate Binding Study

Sample	Absorbance at 400 nm
Blank	
Standards:	
1/500	
1/100	
3/100	
10/100	(r = 0.99998)
PhosLo Tablets #1	
PhosLo Tablets #2	
PhosLo Tablets #3	Average of 3 = 0.889
PhosLo Caplets #1	
PhosLo Caplets #2	
PhosLo Caplets #3	Average of 3 = 0.886

The absorbances of the standard solution are shown to be linear. The PhosLo tablets and caplets have essentially the same absorbance and this indicates that PhosLo tablets and caplets bind phosphate to the same degree.