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APPLICATION NUMBER:

21-823

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-823
Submission Date August 31, 2004, Original; January 13, 2005, N-000-BB
Brand Name ACTONEL[®] [REDACTED]
Generic Names Risedronate sodium and calcium carbonate
Reviewer S.W. Johnny Lau
Team Leader Hae-Young Ahn
OCPB Division DPE II (HFD-870)
ORM Division Metabolic and Endocrine (HFD-510)
Sponsor Procter & Gamble Pharmaceuticals, Inc.
Relevant IND 31,029
Submission Type; Code Original; S
Formulation; Strength(s) Copackaged oral 35 mg risedronate tablet + 1250 mg CaCO₃ tablet
Indication To treat and prevent osteoporosis [REDACTED]

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1 Executive Summary

The sponsor submitted NDA 21-823 to seek approval for the copackaged oral weekly 35 mg risedronate tablet and oral daily (for the remaining 6 days of the weekly treatment cycle) 1250 mg calcium carbonate tablet for the following proposed indications:

- to treat osteoporosis in postmenopausal women
 - to prevent osteoporosis in postmenopausal women
- [REDACTED]

2 Question-Based Review

2.1 General Attributes

2.1.1 What are the formulation for the to-be-marketed 35 mg risedronate and 1250 mg calcium carbonate tablets?

The sponsor will not change the components, composition, manufacturing sites, manufacturing process, or specification for the approved 35 mg risedronate tablet, which is the to-be-marketed 35 mg risedronate tablets. Table 1 below details the to-be-marketed 1250 mg calcium carbonate tablet's composition as:

Ingredient	Function	Unit Quantity (mg/tablet)
Calcium carbonate, USP	Active	1250.0 ^{ab}
Pregelatinized starch, NF		
Sodium starch glycolate, NF		
Magnesium stearate, NF		
FD&C Blue #2 Aluminum Lake		
Subtotal		
Polyethylene glyco.		
Hypromellose		
Opaspray Blue		
Polysorbate 80, NF		
Purified water, USP ^d		
Subtotal		

Target Total Film-Coated Tablet Weight = 1392.4 mg

a Equivalent to 500 mg elemental calcium.

2.1.2 What is NDA 21-823's proposed indication and dosage regimen?

To treat and prevent osteoporosis in postmenopausal women. Patients should orally take a 35 mg risedronate tablet once a week and then orally take a 1250 mg calcium carbonate tablet daily for the remaining 6 days of the 7-day treatment cycle.

2.2 General Clinical Pharmacology

Risedronate's clinical pharmacology information is available in:

- Dunn and Goa. Risedronate: a review of its pharmacological properties and clinical use in resorptive bone disease. *Drugs* 61:685-712 (2001)
- J.H. Lin. Bisphosphonates: a review of their pharmacokinetic properties. *Bone* 18:75-85 (1996)

Calcium's clinical pharmacology information is available in:

- Rodriguez-Martinez et al. Role of Ca²⁺ and vitamin D in the prevention and treatment of osteoporosis. *Pharmacol Ther* 93:37-49 (2002)

2.2.1 How are the risedronate and calcium doses selected for the copackaged product?

The proposed oral 35 mg risedronate weekly dosing via the copackaged product is the same as the approved oral 35 mg risedronate alone tablet weekly dosing. The NIH Consensus Conference report (*JAMA* 272:1942-8 (1994)) recommends oral daily 1000 – 1500 mg elemental calcium intake for postmenopausal women. The proposed oral 500 mg elemental calcium daily dosing contributes to part of the recommended daily elemental calcium intake for postmenopausal women.

2.3 General Biopharmaceutics

2.3.1 Does difference exist between the to-be-marketed formulation and the clinically-tested formulation?

No. The to-be-marketed risedronate tablet in the copackaged product is the same as the approved 35 mg risedronate tablet. The to-be-marketed calcium carbonate tablet is the same as the calcium carbonate tablet that was used in the pivotal clinical Phase III studies that supported risedronate's NDA 20-835/S001.

2.3.2 What is evidence that supports the in vivo bioavailability of the to-be-marketed 1250 mg calcium carbonate tablet?

The key clinical pharmacology and biopharmaceutics issue for this copackaged 35 mg risedronate tablet and 1250 mg calcium carbonate tablet product is to establish the evidence of in vivo bioavailability for its calcium component, which can be shown via (see Attachment):

- CFR 320.24(b)(4) Well-controlled clinical trials in humans that establish the safety and effectiveness of the drug product, for purposes of establishing bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence. Reasons:
 - The sponsor used identical formulation as the to-be-marketed calcium carbonate tablet in the Phase III pivotal studies for NDA 20-835/S-001 of 5 mg risedronate daily in the treatment and prevention of postmenopausal osteoporosis. The manufacturing and testing specifications of these calcium carbonate tablets met USP acceptance criteria.

2.3.3 What is the proposed in vitro dissolution test and acceptance criterion for the calcium carbonate tablet?

The sponsor proposed the USP test monograph for calcium carbonate tablets and its in vitro dissolution method and acceptance criterion follow (Table 2):

	Calcium Carbonate
Apparatus	USP Type 2 (paddle)
In vitro dissolution medium	0.1 N hydrochloric acid
Volume of dissolution medium	900 mL
Medium temperature	37 ± 0.5°C
Stirring speed	75 rpm
Sampling Time	30 minute
Acceptance criterion	Not less than Q (Q) of the labeled amount of CaCO ₃ is dissolved in 30 minutes

2.4 Analytical

Are the bioanalytical methods used to support NDA 21-823 acceptable?

Not applicable since no clinical study was conducted.

9 Page(s) Withheld

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 Deliberative Process

Withheld Track Number: Clin Pharm/Bio-1

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission				
	Information		Information	
NDA	21-823	Brand Name	ACTONEL [®] [REDACTED]	
OCPB Division	2	Generic Name	Risedronate Na + CaCO ₃	
Medical Division	DMEDP, HFD-510	Drug Class	Bisphosphonate + Ca	
OCPB Reviewer	S.W. Johnny Lau	Indication(s)	Treat/prevent osteoporosis + [REDACTED]	
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Copackaged tablets	
Date of Submission	30-AUG-2004	Dosing Regimen	1 ACTONEL [®] tab/week & 1 CaCO ₃ tab/day	
Estimated Due Date of OCPB Review	5-MAY-2005	Route of Administration	Oral	
Division Due Date	26-MAY-2005	Sponsor	P&G Pharmaceuticals, Inc.	
PDUFA Due Date	30-JUN-2005	Priority Classification	Standard	
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies				
HPK Summary				
Labeling	x			Published literature: 11 articles for Clinical Pharmacology section; 7 articles for Drug Interactions section
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	X	1		Published book chapter
Pharmacokinetics (e.g., Phase I) -				
<i>Healthy Volunteers-</i>				
single dose:	X	2		Published literature
multiple dose:				
<i>Patients-</i>				
single dose:	X	3		Published literature
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	4		Published literature
In-vivo effects of primary drug:	X	3		Published literature
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:	X	1		Published literature
pediatrics:				
geriatrics:	X	1		Published literature
renal impairment:				
hepatic impairment:				
Achlorhydria	█	█		Published literature
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				

Population Analyses -			
	Data rich:		
	Data sparse:		
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
Bioequivalence studies -			
	traditional design: multi dose:		
	replicate design: single / multi dose:		
Food-drug Interaction studies:			
Dissolution:			
(IVIVC):			
Bio-wavler request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		18	Published literature
Fiability and QBR comments			
	"X" if yes	Comments	
Application filable ?	X		
Comments sent to firm ?	X	<ul style="list-style-type: none"> • Did the in vitro dissolution of the calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval meet the USP acceptance criteria? • Were the calcium carbonate tablets that were used in the pivotal clinical studies for risedronate's original NDA approval identical to the to-be-marketed calcium carbonate tablets for NDA 21-823? 	
QBR questions (key issues to be considered)			
Other comments or information not included above			
Primary reviewer Signature and Date			
Secondary reviewer Signature and Date			

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/s/

S.W. Johnny Lau
11/9/04 07:19:55 PM
BIOPHARMACEUTICS

Hae-Young Ahn
11/29/04 10:54:49 AM
BIOPHARMACEUTICS

Filing Memo

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

NDA: 21-823
Compound: Risedronate sodium plus calcium carbonate (ACTONEL[®] [redacted])
Sponsor: P & G Pharmaceuticals, Inc.
Submission Date: August 30, 2004
From: S. W. Johnny Lau, R.Ph., Ph.D.

Background

The sponsor submitted NDA 21-823 to seek approval for the copackaged weekly oral 35 mg risedronate + daily oral 1250 mg calcium carbonate (except the day taking risedronate) tablets to:

- treat osteoporosis in postmenopausal women
 - prevent osteoporosis in postmenopausal women
-

The sponsor markets the weekly oral 35 mg risedronate tablet (ACTONEL[®]), which has the following indications:

- treatment of osteoporosis in postmenopausal women
 - prevention of osteoporosis in postmenopausal women
 - prevention and treatment of glucocorticoid induced osteoporosis
 - treatment of Paget's disease
-

[redacted] that the calcium component of ACTONEL[®] [redacted] is a new drug product.

Findings

The sponsor:

- did not conduct any study to support NDA 21-823
- referenced NDA 21-823's Human Pharmacokinetics and Bioavailability section to that of NDA 20-835's. ACTONEL[®]'s approval is under NDA 20-835.
- proposed labeling with annotation for calcium
- provided 11 and 7 published articles to support the Clinical Pharmacology and Drug Interactions sections, respectively, for the calcium labeling changes from the ACTONEL[®] label.
- stated that "The drug product will meet USP criteria for calcium carbonate tablets." The USP does have a monograph for calcium carbonate tablet, which has the in vitro dissolution method and acceptance criteria (tolerance).

The filing meeting was on October 7, 2004.

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S.W. Johnny Lau
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Hae-Young Ahn
6/14/05 11:23:33 AM
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