CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-835/S001-004

ADMINISTRATIVE DOCUMENTS

DEC 22 1998

NDA 20-835/S-001, S-002, and S-003

Procter & Gamble
Attention: Linda Manning, Pharm.D.
Senior Scientist, Regulatory Affairs
Sharon Woods Technical Center
11450 Grooms Road
Cincinnati, OH 45242-1434

Dear Dr. Manning:

We acknowledge receipt of your efficacy supplemental applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Actonel (risedronate sodium) Tablet

NDA Number: 20-835

Date of Supplements: December 18, 1998

Date of Receipt: December 18, 1998

Supplement Number: S-001

This supplement proposes the following change: Actonel is indicated to maintain or increase BMD in men or women who are either initiating or continuing long-term, systemic corticosteroid treatment for chronic diseases.

Therapeutic Classification: Priority (P)

Supplement Number: S-002

This supplement proposes the following change: Actonel is indicated for the prevention of postmenopausal osteoporosis

Therapeutic Classification: Standard (S)

Supplement Number: S-003

This supplement proposes the following change: Actonel is indicated for the treatment of postmenopausal osteoporosis

Therapeutic Classification: Standard (S)

We unbundled your submission into three supplements because each indication must be the subject of a separate supplement.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these application will be filed under section 505(b) of the Act on February 16, 1999, in accordance with 21 CFR 314.101(a). If supplement 001 is filed, the user fee goal date will be June 18, 1999; if supplements 002 and 003 are filed, the primary user fee goal date will be October 18, 1999.

All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

/S/ 12.21.98

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Patent Information Statement Pursuant to 21 USC 355(b)

The drug for which this application is submitted is claimed in U.S. Patent 5,583,122, issued December 10, 1996, assigned to The Procter & Gamble Company (the parent company of Procter & Gamble Pharmaceuticals, Inc.) This patent expires December 10, 2013.

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Checklist

NDA:	21-935/S-001, S-002, S-003, S-004
Trade Name:	Actonel
Generic Name:	risedronate sodium
Applicant Name:	Procter & Gamble
Division:	HFD-510
Project Manager:	Randy Hedin
Approval Date:	

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a. Is it an original NDA?	Yes		No	✓
b. Is it an effectiveness supplement?	Yes	✓	No	
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Explanation:

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

Explanation:

d. Did the applicant request exclusivity?	Yes	✓	No	
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?	3 years			

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	✓
If yes, NDA #				
Drug Name:				

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes	✓	No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	Risedronate Sodium
NDA #	20-835
Drug Product	
NDA #	
Drug Product	
NDA #	

2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes		No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	

NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	✓	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	✓	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	✓
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:	Studies RCP + RCT			
Investigation #2, Study #:	Studies RVN + RVE			
Investigation #3, Study #:	Studies RBL + RPE			
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	✓
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	✓
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the				

application or supplement that is essential to the approval (i.e., the investigations listed in #2 (c), less any that are not "new"):

Investigation #1	RCP, RVN
Investigation #2	RVE, RCT
Investigation #3	RBL, RPE

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes	✓	No	
IND#:	—			
Explain:				
Investigation #2	Yes	✓	No	
IND#:	—			
Explain:				
Investigation #3	Yes	✓	No	
IND#:	—			
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

BACK TO TOP

Signature of PM/CSO /S/

Date: 4/13/00

Signature of Division Director /S/

Date: 4/14/00

cc:

Original NDA

Division File

HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

BACK TO TOP

Exclusivity Statement

Requesting Three Years of Exclusivity

As part of this supplemental new drug application, Procter & Gamble Pharmaceuticals (P&GP) is requesting three years exclusivity for the use of ACTONEL (risedronate sodium tablets) for the treatment and prevention of postmenopausal osteoporosis and for corticosteriod-induced osteoporosis. P&GP is the sole developer of this chemical entity and owns the patent rights.

Pursuant to §§ 314.50(j) and 314.108(b)(5), support for this exclusivity request is based on the following:

1. P&GP has previously received marketing approval for the use of Actonel in the treatment of Paget's disease of bone. Approval was given by FDA on March 27, 1998.

2. P&GP has submitted reports of new clinical investigations that are essential to approval of Actonel for these new indications.

NDA 20-835/S-001, S-002, S-003, S-004
Actonel (risedronate sodium) Tablets
Procter and Gamble

The submission was received before financial disclosure was mandated.

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20835	**Trade Name:**	ACTONEL (RISEDRONATE SODIUM) 30MG TABS
Supplement Number:	3	**Generic Name:**	RISEDRONATE SODIUM
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	The treatment of postmenopausal osteoporosis.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The indication is for treatment of postmenopsusal osteoporosis and would be inappropriate for pediatric patients.
04/13/00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/ 4/13/00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20835	**Trade Name:**	ACTONEL (RISEDRONATE SODIUM) 30MG TABS
Supplement Number:	2	**Generic Name:**	RISEDRONATE SODIUM
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	The prevention of postmenopausal osteoporosis.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The indication is for prevention of postmenopausal osteoporosis and would be inappropriate for pediatric patients.
4/13/00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/

Signature

4/13/00

Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20835	**Trade Name:**	ACTONEL (RISEDRONATE SODIUM) 30MG TABS
Supplement Number:	1	**Generic Name:**	RISEDRONATE SODIUM
Supplement Type:	SE1	**Dosage Form:**	Tablet; Oral
Regulatory Action:	AP	**Proposed Indication:**	The treatment of glucocorticoid induced osteoporosis

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The Division feels that the benefit of trials in a pediatric population would not be worth the long-term risk. 4.13.00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/ 4/13/00

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20835	**Trade Name:**	ACTONEL (RISEDRONATE SODIUM) 30MG TABS
Supplement Number:	4	**Generic Name:**	RISEDRONATE SODIUM
Supplement Type:	SE1	**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	The prevention of corticosteroid-induced osteoporosis.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

The Division feels that the benefit of trials in a pediatric population would not be worth the long-term risk. 4.13.00

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/ 4/13/00

Signature Date

Certification Pursuant to the Generic Drug Enforcement Act of 1992

Pursuant to 21 USC §355a(k)1, Procter & Gamble Pharmaceuticals hereby certifies it has not and will not use in any capacity the services of any person debarred under subsection 21 USC §355a(a or b), in connection with this supplemental New Drug Application.

Respectfully submitted,

Larry R. Versteegh, Ph.D.
Vice President
Regulatory and Clinical Development
Procter & Gamble Pharmaceuticals

APPEARS THIS WAY
ON ORIGINAL

10/14/99 Division Director's memo incorporated into the substance of the approvable letter

/S/

APPEARS THIS WAY
ON ORIGINAL

Dw file

SEP 16 1999

NDA 20-835/S-004

Procter & Gamble Company
Attention: Linda W. Manning
Senior Scientist, Regulatory Affairs
Health Care Research Center
P.O. Box 8006
Mason, Ohio 45040-8006

Dear Ms. Manning:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Actonel® (risedronate sodium) Tablets
NDA Number:	20-835
Supplement Number:	S-004
Therapeutic Classification:	To be determined at filing meeting
Date of Supplement:	August 27, 1999
Date of Receipt:	August 30, 1999

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 29, 1999, in accordance with 21 CFR 314.101(a).

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). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study 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) 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 proceed with the pediatric drug development plan that you submit, and notify you of the pediatric studies that are required under section 21 CFR 314.55. 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.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

/S/ 9.16.99

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL