

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020835

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

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NDA: 20-835

SUBMISSION DATE: February 11, 1997
May 29, 1997
March 31, 1997
December 05, 1997
December 12, 1997
December 19, 1997 (2 submissions)**BRAND NAME:** ACTONEL™**GENERIC NAME:** Risedronate sodium, 30 mg tablets**REVIEWER:** Carolyn D. Jones, Ph.D.
Robert M. Shore, Pharm.D.**SPONSOR:** Procter & Gamble Pharmaceuticals, Inc.,
Norwich, NY**Type of Submission:** Original NDA (NME) **Code: 1S**

SYNOPSIS:APPEARS THIS WAY
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A request for a change in label was made by Dr. Troendle to clarify the section on renal impairment.

Current statement:

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Renal Insufficiency: Risedronate is excreted intact primarily via the kidney. Exposure to risedronate was estimated to increase by 77% in patients with creatinine clearance of 20 mL/min.

Therefore, Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance \leq 30 mL/min)

Proposed change:

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Renal Insufficiency: Risedronate is excreted intact primarily via the kidney. As compared to persons with normal renal function, a 77% decrease in renal clearance was observed in patients with creatinine clearance \leq 20 mL/min.

Therefore,
Actonel is not recommended for use in for patients with severe renal impairment (creatinine clearance \leq 30 mL/min).

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1/28 /98

Carolyn D. Jones, Ph.D.

Robert M. Shore, Pharm.D.

Division of Pharmaceutical Evaluation II

Office of Clinical Pharmacology and Biopharmaceutics

S/S 1/28/98 ✓
01/28/98

RD initialed by Hae-Young Ahn, Ph.D., Team Leader *S*

FT initialed by Hae-Young Ahn, Ph.D., Team Leader *S*

1/28/98

CC: NDA 20-835 (1 copy) HFD-510 (Troendle, Hedin), HFD-340 (Vishwanathan), HFD-870 (Ahn, Jones, Shore, M. Chen), CDR (Murphy).

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Norwich, NY

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SYNOPSIS:

Risedronate (NE-58095) is a pyridinyl bisphosphonate, a member of a series of new bisphosphonate compounds synthesized as analogs of pyrophosphate and intended for use in patients with increased bone turnover such as Paget's disease of bone. Risedronate is chemically described as [1-hydroxy-2-(3-pyridinyl)ethylidene]bis[phosphonic acid] monosodium salt.

Paget's disease of bone is a localized but progressive disorder. Elevated bone turnover and remodeling result in the formation of disorganized and weakened bone. Its prevalence in the United States may be as high as 3% in people over the age of 55 years. Paget's disease rarely presents before the age of 40, with increasing prevalence with age. The clinical presentation of Paget's disease covers the spectrum from asymptomatic disease detected on X-ray or with routine serum chemistry testing, to conditions associated with pain (the most commonly reported symptom), bone deformity, pathological fracture, neuropathy, and high-output cardiac failure.

For patients in whom intervention is indicated, risedronate 30 mg daily for 2 months is the proposed treatment. The sponsor reports that bone turnover is significantly reduced and usually normalized, and patients report improvement in pain. Patients who partially respond to 30 mg risedronate for 2 months, or who relapse as assessed by an increase in serum alkaline

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phosphatase towards pretreatment levels, can be retreated with a second course of 30 mg risedronate for 2 months. Since it has been demonstrated that serum alkaline phosphatase levels continue to decrease for 2 to 3 months after risedronate treatment has been stopped, a decision to retreat should be postponed for at least 2 months after the initial risedronate treatment has been discontinued.

Of the 364 subjects and patients who participated in the various pharmacokinetic studies that were reviewed, 328 were male, and 36 were female. Ages ranged from . Doses of risedronate ranged from taken orally; intravenously administered risedronate ranged from

In early pharmacokinetic studies, only urine was collected for the characterization of risedronate pharmacokinetics due to the lack of a serum or plasma assay. The absolute oral bioavailability of risedronate was approximately 0.65% for both the tablet and the solution based on AUC or A_e . Most of the variability in the pharmacokinetics of risedronate can be attributed to the absorption process. After oral administration, the intra-subject CV for AUC, C_{max} , and A_e is generally greater than the inter-subject CV (~20%). After IV administration, the intra- and inter-subject CV for these pharmacokinetic parameters is approximately 20%.

Risedronate urinary excretion increased dose proportionally over the range of 0.10- 0.50 mg risedronate when given as increasing intravenous doses. Dose proportionality was also observed after oral administration. The median cumulative urinary excretion expressed as a percentage of the dose after a single intravenous dose was 6 in 24 hours and 85% of an IV dose was recovered in the urine over 28 days. Renal clearance (CL_R) comprised 87% of the total CL, and only a small percentage (13%) of a systemically available dose is "cleared" or incorporated into bone. A long $t_{1/2}$ (201 h) was observed. As compared to single dose, urinary excretion increased following 7 days of IV multiple dosing and after 13 days of oral dosing. Risedronate pharmacokinetics were linear following single dose, oral administration over the range of

A food effect study was conducted with risedronate administered 2 h after a meal (generally dinner), 0.5 or 1 h prior to breakfast, or in a fasted state. C_{max} and AUC were 3.3- and 1.4-fold greater, respectively, when risedronate was administered 1 h before breakfast as compared to 2 h after dinner. The phase III pivotal study was conducted with risedronate administration before breakfast and the phase II pivotal study was conducted with risedronate administered two h after a meal.

Similar to other bisphosphonates, *in vitro* metabolism studies with risedronate indicated that no systemic metabolism occurred in humans or animals. The sponsor did not conduct an *in vivo* metabolism study in humans. However, *in vivo* metabolite profiling studies were completed in rats and dogs with no metabolites detected in bone, plasma or pre-bladder urine and about 85% of an IV dose is recovered in the urine as intact risedronate and animal data suggest that some of the remaining drug is cleared into bone.

Two known chemical degradation products were found in rat and dog urine samples after oral dosing which represented less than 0.1% of the oral dose. *In vitro* experiments indicated that the amount of degradation was 1% in human urine incubated at 37°C over 24 h.

Risedronate is highly protein bound in rat (95%), dog (86%), and human (93%) plasma, at concentrations of _____ in rat and dog plasma, and at concentrations of _____ µg/mL in human plasma. Nonlinearity in risedronate protein binding occurred in human plasma as concentrations reached the range of _____

A renal impairment study was conducted. The regression analysis of renal clearance and creatinine clearance indicated a significant correlation; risedronate renal clearance was reduced (77%) with a decrease in creatinine clearance over the range of 120 to 20 mL/min. A decrease (44%) in predicted oral clearance was also observed; however, it appears that one outlier may account for this discrepancy between oral and renal clearance.

To evaluate the effects of age on the pharmacokinetics of risedronate, cross-study comparisons were conducted. The sponsor used 45 years of age as the lower limit for the elderly. However, FDA defines the elderly as persons over 65 years of age. No conclusions could be drawn regarding the effect of age on risedronate pharmacokinetics due to the small number of subjects, cross-study analysis, and the large variability associated with this drug.

The sponsor used the food effects study to evaluate gender. However, no conclusions can be drawn because the sponsor did not evaluate the appropriate pharmacokinetic parameters.

The principal dosage form used in the phase II clinical pharmacology studies was a gelatin capsule. A phase II clinical efficacy trial also used this capsule formulation; the Division of Metabolic and Endocrine Drug Products (DMEDP) has accepted this phase II study as one of the required pivotal clinical studies (See appendix 6). In the second pivotal phase III study, only a cellulose film-coated tablet was used and this tablet is the intended commercial dosage form. The dissolution data generated for 30 mg risedronate sodium film-coated tablets manufactured by the clinical and commercial processes indicated that these dosage forms were similar.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed NDA 20-835 submitted on February 11, 1997, March 31, 1997, and December 05, 1997. The Human Pharmacokinetics Section is acceptable. Please convey recommendation, comments (p. 29) and labeling comments (p. 30) to sponsor as appropriate.

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BACKGROUND:

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Risedronate has a molecular weight of 305.10 and a molecular formula of $C_7H_{10}NO_7P_2Na$ (Figure 1). The pH of a 1.0% aqueous solution of risedronate sodium is 4.15.

The bisphosphonate drugs differ structurally from pyrophosphate in that a P-C-P bond replaces the P-O-P bond. This P-C-P chemical structure is much less susceptible to hydrolysis than the P-O-P bond and allows for both extended biological activity in bone and absorption as an intact drug from the gastrointestinal tract. The relationship to pyrophosphate can be demonstrated by the bisphosphonates' ability to inhibit hydroxyapatite dissolution *in vitro*.

Other previously developed bisphosphonates, such as etidronate, clodronate, pamidronate, and alendronate have demonstrated potent effects on the skeleton through inhibition of bone resorption in a variety of *in vivo* models. These compounds have been proven to be clinically

useful in several bone disorders, particularly Paget's disease, hypercalcemia of malignancy, and osteoporosis.

During the course of development of risedronate several meetings were held between the FDA and the sponsor. In regards to biopharmaceutic issues several points were discussed. During the meeting of September 5, 1996, the sponsor was asked the following questions:

1) Whether any specific drug-drug interactions were planned? RESPONSE: no. The sponsor did state that during the pivotal trials concurrent medications were allowed during the treatment period. The sponsor agreed that this information would be broken out in the integrated studies of summaries (ISS).

2) Whether any specific gender studies were conducted? RESPONSE: no. However, both males and females participated in the various pharmacokinetic studies and the data would be analyzed for differences.

3) The sponsor stated no pharmacokinetic data in patients would be submitted.

4) In response to a question regarding dissolution data, the sponsor stated that dissolution profiles at multiple pH values would be submitted and no *in vivo/in vitro* correlation would be performed.

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PROTOCOL INDEX

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91014	Bioavailability of a Single Dose of Risedronate Solution (NE-58095) when Administered Duodenally at Two Different Concentrations and Rates to Normal, Healthy, Male Volunteers (August 1991)	52

RAB011594	A Study to Determine the Absolute Bioavailability of Risedronate After the Administration of a Single 30 mg Tablet, a Single 30 mg Oral Solution and a 0.3 mg Intravenous Dose to Normal Healthy Volunteers (April 1995 - September 1995)	54
N/A	Equivalence of Commercial and Clinical Risedronate Sodium Film-Coated Tablets, 30 mg	N/A
90011	A Double-Blind, Placebo-Controlled Phase I Study to Determine the Safety and Tolerance of Intravenous Risedronate (NE-58095) in Healthy Adult Male Volunteers (July 1990 - September 1990)	57
1994022	A Study to Evaluate the Duration of Sample Collection Necessary to Characterize the Pharmacokinetics of Risedronate after Single Dose, Oral Administration of 30 mg to Normal Healthy Volunteers (March 1994 - April 1994)	59
92016	Study to Evaluate Carryover Effect and Intra-Subject Variability for Risedronate Dosage Forms (July 1992 - August 1992)	61
88020	A Double-Blind, Placebo-Controlled Rising Multiple Dose Study To Determine the Safety and Tolerance of Oral Doses of NE-58095 in Adult Male Volunteers (June 1988 - September 1988)	63
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the relationship to meals following oral administration of a single 30 mg dose to normal healthy volunteers. Risedronate was orally administered using a single dose, randomized, parallel study design to healthy male and female volunteers. All subjects were administered a single oral 30 mg dose (3x10 mg tablets) of risedronate with 240 mL of water either fasted, 0.5 hour or 1 hour after breakfast, or 2 hours after dinner. Venous blood and urine were collected from each subject immediately prior to dosing and for 168 h postdose; was used to estimate pharmacokinetic parameters.

The extent of absorption (AUC, A_e) was not statistically significantly different between dosing 2 h after dinner and 0.5 h before breakfast; however, C_{max} was 2.5-fold greater when risedronate was administered 0.5 h before breakfast. C_{max} and AUC were 3.3- and 1.4-fold greater, respectively, when risedronate was administered 1 h before breakfast as compared to 2 h after dinner. These results indicate that the phase III dosing regimen may provide equal or greater exposure to risedronate than the phase II dosing regimen.

It is important to note that there is no *in vivo* bioequivalence data for 3x10 mg as compared to 1x30 mg tablets, and the formulations are not proportional. However, there does appear to be similarity in the pharmacokinetic parameters for tablet, capsule, and solution formulations (risedronate has high solubility and low permeability). Therefore, it may be reasonable to assume that the 3x10 mg dose would reflect a 1x30 mg dose *in vivo*.

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III. Metabolism

In vitro metabolism studies of risedronate with liver slices, plasma, serum and fecal flora suggested that no systemic metabolism occurs in humans or animals (dogs and rats). No metabolites were detected in bone, plasma or pre-bladder urine (collected via ureteral cannula) from rats dosed orally or intravenously with risedronate.

Three known chemical degradation products, 1-oxo-2-(3-pyridinyl)ethylidene]phosphonic acid(keto), 1-hydroxy 2-(3-pyridinyl)-ethylidene]phosphonic acid (hydroxy) and 3-pyridyl acetic acid (3-PAA) were found in human, rat and dog urine samples after oral dosing. These amounts represented less than 0.1% of the oral dose. A fourth peak was observed which was thought to be a chromatographic artifact or another degradant. *In vitro* experiments indicated that the amount of degradation was 1% in human urine incubated at 37°C over 24 h. No degradation occurred in urine stored at 5°C. A 10-fold increase in degradation product was observed in the rat compared to the human.

The reviewer is in agreement with the sponsor's conclusions that there is no data to demonstrate systemic metabolism of risedronate. However, only one human liver was used in the liver slice analysis and because of intersubject variability, more human livers would have made a more substantial argument. For the fecal analysis, 5 humans donated fecal samples which was an adequate number.

No evidence of hepatic microsomal enzyme induction was detected in rats dosed daily with risedronate for 14 days. No drug-related increases in liver weight, cytochrome P450 content or catalytic activity, or in UDP-glucuronosyltransferase activity were detected.

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IV. Dose Proportionality

Study RSD005794 was a single-center study with a double-blind, randomized, parallel study design in healthy male (n=61) and female (n=6) subjects. Subjects were orally administered either 2.5, 5, or 30 mg of risedronate as cellulose-film-coated tablets with 240 mL of water. Blood and urine were collected for 3 and 28 days, respectively. As Figure 5 demonstrates, risedronate in serum was difficult to quantitate at lower doses; this same trend is seen with the urine assay (plot not included here). As such, an estimate of the terminal half-life and V_z using the lower doses may not correspond to estimates using higher doses.

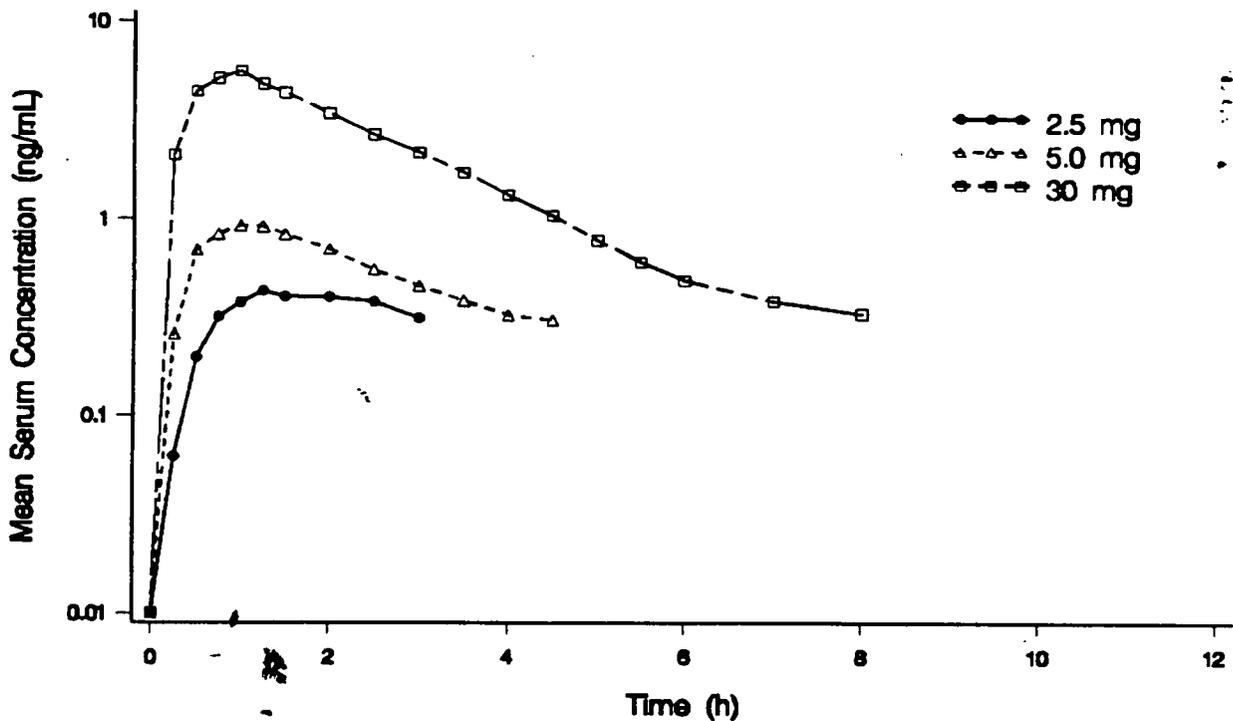


Figure 5: Mean risedronate serum concentration-time profile following a single oral tablet dose (Study RSD005794).

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As Figure 6 demonstrates C_{max} was proportional with dose over the range of , AUC plots were similar and thus are not included here.

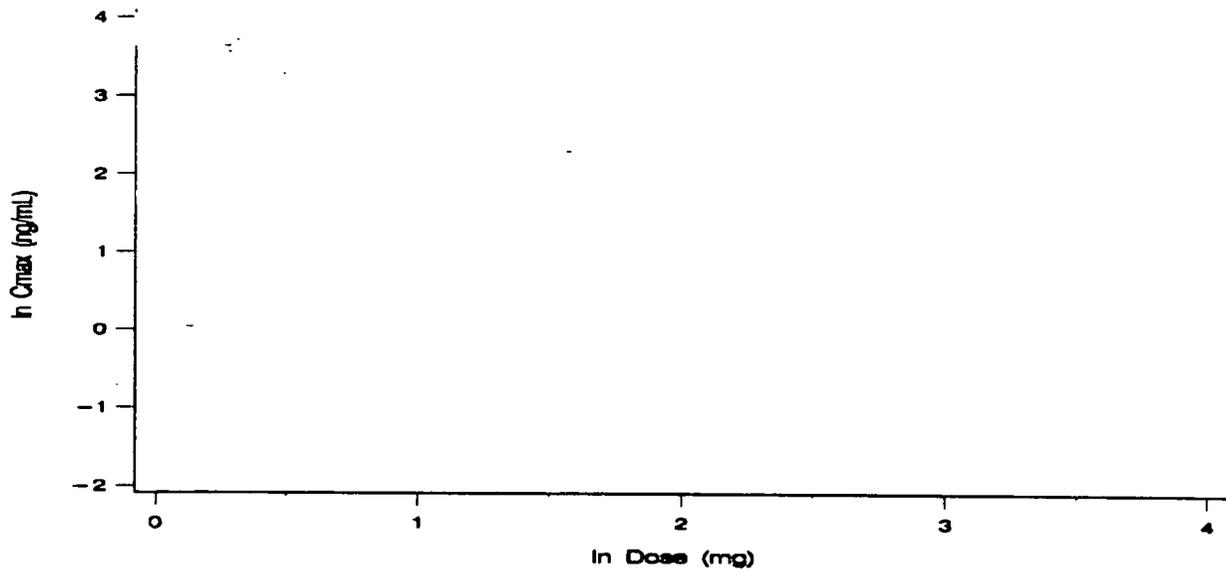


Figure 6: Dose proportionality of C_{max} after single oral tablet dose (study RSD).

V. Special Populations

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A. Renal Impairment

Study RRI was a single-center study with an open-label, single-dose, balanced parallel study design in which 21 subjects (7 females, 14 males) with varying degrees of renal impairment received a single 30-mg dose of risedronate. The mean age at screening was 59.7 years. Venous blood and urine samples were collected and analyzed.

The degree of renal impairment was classified according to the following ranges:

Group	Creatinine clearance
I	>80 mL/min
II	50-80 mL/min
III	30-49 mL/min
IV	<30 mL/min

Subjects were assigned in the following manner to the 4 groups: 6 subjects in Group I, 6 subjects in Group II, 6 subjects in Group III and 3 subjects in Group IV.

The regression analysis of renal clearance and creatinine clearance (the method of analysis suggested in the Renal Guidance) indicated a significant correlation between renal function and the clearance of risedronate (Figure 7). Risedronate renal clearance was reduced (77%) with a decrease in creatinine clearance over the range of 30-80 mL/min. Consistent with renal clearance was a trend toward a lower oral clearance when creatinine clearance was decreased. This trend was the consequence of a reduction in renal clearance which resulted in a decrease (44%) in predicted oral clearance. However, when one subject with a very low AUC

value was removed from the analysis, the oral and renal clearances showed similar reductions.

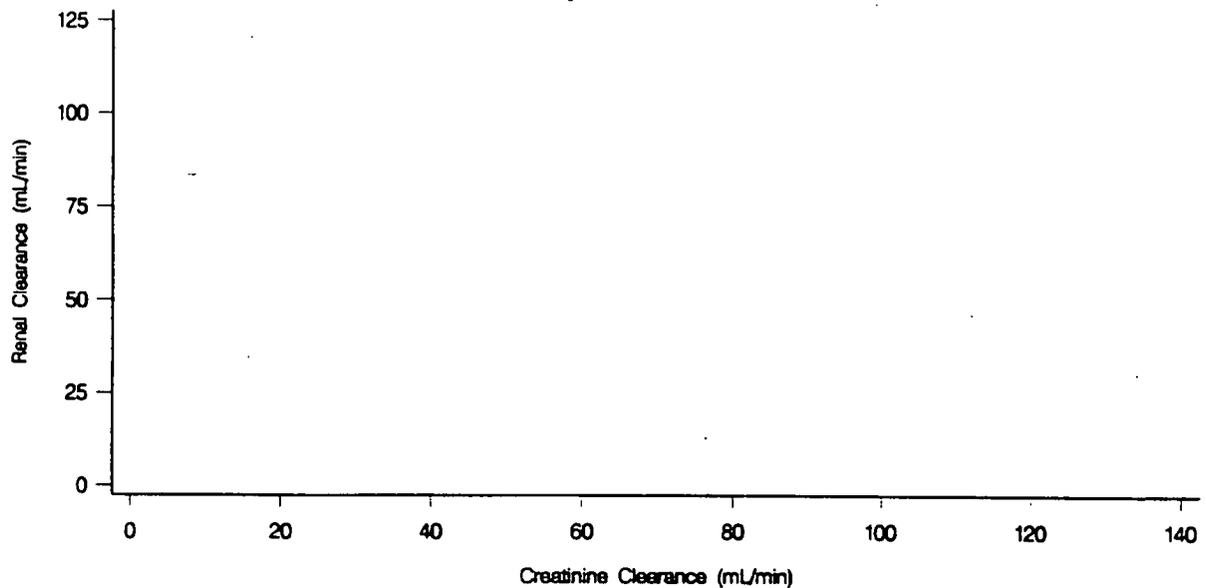


Figure 7: Plot of Cl_{cr} versus CL_R for study RRI.

Note in the plot that the mildly impaired group is extremely variable and contains points that do not follow the general trend of the other data.

The sponsor stated that these results suggest that only patients with severe renal impairment (creatinine clearance < 30 mL/min) could require a dosage adjustment (either decrease the risedronate dose by 50% or double the interval between doses). A decrease in clearance has been reported with tiludronate and clodronate in patients with moderate to severe renal impairment. Tiludronate mean oral clearance decreased 70% in patients with creatinine clearance ranging from . Clodronate mean plasma clearance decreased 50% following intravenous administration to patients with creatinine clearances < 50 mL/min.

The reviewer, however, believes that risedronate should not be used in severely renally-impaired patients. The sponsor has not demonstrated that the recommended dosage adjustment is a safe and efficacious treatment for this population. In the pivotal clinical trials, renally-impaired patients were excluded, therefore no clinical data were available for this population. Furthermore, the Medical Officer has suggested that standard medical practice excludes treatment of severely renally-impaired patients with bisphosphonates; this is reflected in the labeling of currently marketed products.

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Although the regression analysis shows the relationship between Cl_{cr} and Cl_{R_2} , there are currently no pharmacokinetic-pharmacodynamic data that would suggest an *a priori* 'cut-off' for exclusion of certain patients from treatment with risedronate.

Also in the protocol, the sponsor stated that protein binding would be investigated in renally impaired patients. This information was not included as part of the NDA. However, the sponsor in a telecon (December 18, 1997) stated that this analysis is underway and will be submitted to the Agency.

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B. Hepatic Impairment

No *in vitro* evidence of metabolism exists. Therefore, the sponsor did not conduct any *in vivo* hepatic impairment studies.

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Table 12: Risedronate pharmacokinetics after oral dose administration in renally impaired patients (Study RRI)

Subject No.	AUC (ng·h/mL)	C _{max} (ng/mL)	t _{max} (h)	t _{1/2Z} (h)	Cl _O (mL/min)	Cl _O (L/h/kg)	Cl _R (mL/min)	Cl _R (L/h/kg)	V _{Z/F} (L)	V _{Z/F} (L/kg)	A _e (µg)	A _e (%)
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^a AUC is the area under the serum concentration-time profile from time 0 → ∞; C_{max} is the maximum serum concentration; t_{max} is the time that the maximum serum concentration occurs; t_{1/2Z} is the half-life of the terminal exponential phase; Cl_O is the oral clearance; Cl_R is the renal clearance; V_{Z/F} is the terminal volume of distribution, uncorrected for bioavailability; A_e is the cumulative amount of drug excreted in urine from 0 → ∞; and A_e is the cumulative amount of drug excreted in urine normalized for dose and expressed as a percentage.

C. Age

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No individual study was conducted to determine the effect of age on the pharmacokinetics of risedronate. However, the sponsor conducted a cross-study comparison of risedronate pharmacokinetics in elderly (study RRI013294) and young subjects (studies RRF008593, 1994022, RSD005794 and RAB011594). The sponsor stated that this comparison used healthy volunteers with normal renal function. Both serum and urine samples were collected and the dose of risedronate was 1x30 mg tablet orally administered following overnight fast and 4 h prior to a meal.

In this cross-study comparison, a total of 101 subjects were evaluated; 5 of 6 subjects were ≥ 62 years of age. The typical definition of elderly is subjects greater than 65. The young population was less than 45. The renal clearance was decreased 26% and AUC was increased 15% in the elderly, all other parameters were similar (Table 13). However, a formal statistical analysis (e.g., confidence intervals) was not conducted to compare the effect of age on the pharmacokinetics of risedronate. The sponsor states that these differences in pharmacokinetic parameters should have no effect on the clinical response of risedronate in the elderly and therefore, no dosage adjustments are required.

There are a number of inherent problems in this analysis including: 1) the small number of subjects in the elderly population, 2) the cross-study design, and 3) the large variability in risedronate pharmacokinetics. There is currently no guidance for analyzing the effect of age on the pharmacokinetics of a drug, unlike the condition of renal impairment for which a guidance exists. Although several methods have been used and/or proposed (e.g., sub-group analysis and regression analysis), the sample size in this study is too small. With this in mind, the reviewer believes no conclusions can be drawn from this study due to the aforementioned reasons.

Table 13: Mean(SD) Pharmacokinetic Parameters After Single Dose Oral Administration of 30 mg Risedronate to Young and Elderly Volunteers^a

Study Number	Study Population; Age \pm SD; N	Route and Dosage Form	Dose	C _{max} (ng/mL)	t _{max} (h)	AUC (ng·h/mL)	A _e (μ g)	t _{1/2,z} (h)	CL _O (L/h/kg)	CL _R (L/h/kg)	V _{Z/F} (L/kg)
Young											
RRF008593	Male & female subjects; Age 30 \pm 6 y; N=32	PO; tablet	30 mg; single dose	4.20 (1.75)	0.61 (0.44)	16.8 (8.2)	95.2 (43.2)	116 (81)	29.3 (14.2)	0.0777 (0.0174)	4307 (2291)
1994022	Male subjects; Age 30 \pm 6 y; N=7	PO; tablet	30 mg; single dose	4.81 (2.02)	0.80 (0.42)	24.4 (10.3)	181 (67)	308 (181)	19.4 (8.8)	0.0898 (0.0183)	9376 (8699)
RSD005794	Male & female subjects; Age 28 \pm 5 y; N=23	PO; tablet	30 mg; single dose	5.14 (4.77)	0.81 (0.32)	21.3 (19.1)	258 (148)	224 (44)	27.5 (15.9)	0.195 (0.107)	8493 (4822)
RAB011594	Male & female subjects; Age 33 \pm 8 y; N=32	PO tablet	30 mg single dose	6.22 (6.10)	1.02 (0.35)	33.4 (23.8)	205 (137)	225 (74)	18.7 (13.1)	0.0904 (0.0364)	5811 (3368)
Elderly											
RR1013294	Male & female subjects; Age 64 \pm 10 y; N=7	PO; tablet	30 mg; single dose	6.30 (3.83)	0.99 (0.35)	38.8 (27.2)	189 (120)	215 (89)	13.8 (7.5)	0.0854 (0.0107)	3913 (2337)

^a N is the number of subjects used to estimate the mean; AUC is the area under the serum concentration-time profile from time 0 \rightarrow ∞ , unless otherwise indicated; C_{max} is the maximum serum concentration; A_e is the cumulative amount of drug excreted in urine from time 0 \rightarrow ∞ , unless otherwise indicated; t_{max} is the time that the maximum serum concentration occurs; t_{1/2,z} is the half-life of the terminal exponential phase; CL_R is the renal clearance; CL_O is oral clearance for oral doses; V_{Z/F} is the terminal volume of distribution uncorrected for bioavailability for oral doses.

D. Gender

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A food effect study (Study RRF008593) had 17% (N=22) female subjects recruited and the sponsor used this study to evaluate the influence of gender on risedronate terminal half-life. In this study, risedronate t_{1/2,z} was compared between genders following oral administration of a 30 mg dose at 4 h (Group 1), 1 h (Group 2) and 0.5 h (Group 3) before a meal and at 2 h after dinner

(Group 4). The sponsor stated that no significant differences in gender were observed for three of the four groups (Groups 1, 2 and 4). Although there is a significant difference in median $t_{1/2,z}$ between male and female subjects in Group 3, it is not thought that $t_{1/2,z}$ is sensitive enough to detect a meaningful difference (Table 14).

The sponsor did not evaluate the appropriate pharmacokinetic parameters (i.e., AUC, C_{max} , A_e , and CL_R). Instead the sponsor only examined the effect of gender on the terminal half-life. A summary table (Table 14) was supplied; however, no confidence intervals or point estimates for the comparison of gender were calculated. Therefore, no conclusions can be made.

Table 14: The Effect of Gender on Risedronate Terminal Half-life.

	Group 1	Group 2	Group 3	Group 4
Sex	Dosed 4 h Before Lunch	Dosed 1 h Before Breakfast	Dosed 1/2 h Before Breakfast	Dosed 2 h After Dinner
Female (N)	88.4 (5)	95.1 (5)	44.8 (6)	76.4 (6)
Male (N)	89.2 (27)	92.6 (26)	69.8 (25)	74.3 (26)

$t_{1/2,z}$ is the terminal exponential half-life; N is the number of subjects per treatment group.

VI. Drug Interactions

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In vitro

In vitro studies were conducted to assess the protein binding characteristics of risedronate. In the first study, protein binding was independent of drug concentration for the rat and dog over a () In humans, protein binding averaged 93% from (), but progressively decreased to 83.6% and 67.6% as drug levels increased to 1.0 and 10 $\mu\text{g/mL}$, respectively, demonstrating a nonlinearity in binding. Albumin was probably not involved in this saturation mechanism because the physiological concentration of albumin is 15-fold greater than the highest concentration of risedronate evaluated. In an earlier study, only () of protein binding was attributed to albumin over this same concentration range. No specific gender or erythrocyte/plasma partition information was provided.

A second protein binding study, conducted under similar conditions as the first, demonstrated that plasma protein binding was 98%, 37%, and 24% in the rat, dog and human, respectively. Because of this extreme discrepancy, with little explanation from the sponsor, the Division of Scientific Investigation (DSI) will be requested to audit these studies.

Table 15: Summary of Protein Binding Information

Plasma Source	% NE-58095 Bound						
	Concentration (µg/ml)						
	0.01	0.05	0.10	0.25	0.75	1.0	10
Rat	94.2 ± 4.66 ^a	93.1 ± 0.69 ^a	ND	ND	93.2 ± 0.39 ^a	ND	96.4 ± 0.50 ^a
Dog	84.8 ± 1.14 ^a	ND	83.8 ± 1.28 ^{ab}	ND	ND	86.7 ± 1.23 ^{ab}	87.2 ± 1.62 ^b
Human	93.7 ± 0.56 ^a	90.3 ± 3.01 ^{ab}	ND	95.0 ± 0.61 ^a	ND	83.6 ± 4.46 ^b	67.6 ± 4.31 ^c

Values are Mean ± SD (n=3-7); ND=Not determined

Unlike superscripts represent significant differences between pairs (p<0.05 level)

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No *in vivo* drug interactions were conducted.

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VII. Pharmacokinetic/Pharmacodynamic Relationships

There were no studies that investigated the relationship between pharmacokinetics and pharmacodynamics.

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COMMENTS FROM THE MEDICAL OFFICER REGARDING THIS SUBMISSION:

The medical officer, Sam Dutta, believes risedronate is similar to the other bisphosphonates on the market. It shows some efficacy and there are no major safety concerns. The drug will be most likely recommended for approval. It will not be going to an advisory committee.

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COMMENTS TO BE SENT TO THE FIRM:

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1. For future studies ^{it should be understood} ~~understand~~ that an elderly population is defined as persons ≥65 years of age. Due to the small sample size, cross-study analysis, and large variability associated with this drug, no conclusions about the effect of age on risedronate pharmacokinetics can be made.
2. In study RAB011594 and 92016, intra- and inter-subject variability were examined in subjects

who were administered either a 30 mg tablet or a 10 mg capsule. For both studies the C_{max} was about . Please explain why dose does not affect C_{max} .

3. As a result of the renal impairment study, a recommendation has been made by the sponsor that "a dosage adjustment (dosing every other day) should be considered with appropriate clinical monitoring" in severely impaired patients. The sponsor has not submitted any data to support this labeling statement. Please submit supporting data.

4. There is little multiple dose data in this submission and none of it was generated with the to-be-marketed 30 mg formulation. It is suggested that the sponsor conduct simulations using the appropriate pharmacokinetic model to evaluate accumulation with multiple dosing of this formulation.

5. Only $T_{1/2}$ was analyzed in the age study. It is suggested that the sponsor re-analyze these data using the appropriate pharmacokinetic weight-normalized parameters (e.g., AUC, A_e , C_{max} , and CL_R). The sponsor should contact ~~OCPB~~ *the office of Clinical Pharmacology and Biopharmaceutics* for further discussion regarding this analysis.

6. The sponsor should conduct *in vitro* drug-drug interaction studies as a Phase IV commitment. Although it appears that risedronate itself is not metabolized, its affect on CYP450 pathways has not been elucidated. Risedronate may demonstrate inhibition/induction of enzyme pathways, thereby affecting the metabolism of other drugs that may be given concomitantly (See the discussion on the bottom of page 5 of the Guidance for Industry, Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro "Assessing effects on other drugs." located on the Internet at <http://www.fda.gov/cder/guidance/index.htm>)

LABELING COMMENTS:

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(~~Strikeout text~~ should be removed from labeling; ~~Redline text~~ should be added to labeling; Boxed text is for explanation only and is not intended to be included in the labeling).

1) Pharmacokinetics:

Absorption: Mean ~~oral~~ bioavailability of the tablet is 0.63 (90%CI: 0.54-0.75)...

RAB011594 data for AUC0-inf of the tablet vs. IV formulation from the table in Vol 1.068/p49. The 'mean' is the geometric mean.

Distribution: ...Human plasma protein binding of drug is is unknown.

Two studies were conducted that evaluated human plasma protein binding. The results were very equivocal and an audit of the two studies is underway. Therefore, no information can be included in the label at this time.

Excretion: Approximately half of the absorbed dose is excreted in urine within 24 hours, and 85% of an IV dose is recovered in the urine over 28 days. Mean renal clearance is 105 mL/min (CV=34%) and mean total clearance is 122 mL/min (CV=19%), with the difference primarily reflecting nonrenal clearance or clearance due to adsorption to bone.

RAB011594 data for the tablet formulation from the table in Vol 1.068/p35. The sponsor has supplied calculations of: 1) conversion from L/h/kg to mL/min, and 2) CV.

2) Gender:

risedronate pharmacokinetics is unknown.

The effect of gender on

Only terminal half-life was evaluated in this study. This is an insensitive parameter and more appropriate parameters would be AUC, C_{max} , A_e , and CL_R . See Comment 5.

3) Geriatric:

The effect of age on risedronate pharmacokinetics is unknown.

Small sample size, cross-study analysis, and large variability associated with this drug prevented conclusions from being made.

4) Renal Insufficiency: Risedronate is excreted intact primarily via the kidney. Exposure to risedronate was estimated to increase by 77% in patients with creatinine clearance of 20 mL/min.

Therefore, Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance \leq 30 mL/min).

General: Hypocalcemia and other disturbances of bone and mineral metabolism should be effectively treated before starting ACTONEL therapy. Asymptomatic and clinically insignificant mild decreases in serum calcium and phosphorus levels have been observed in some patients. Adequate intake of calcium and vitamin D should be maintained particularly in patients with Paget's disease in whom bone turnover is significantly elevated. ACTONEL should be used with caution in patients with a history of upper GI disorders. Actonel is not recommended for use in patients with severe renal impairment (creatinine clearance \leq 30 mL/min)

(And also **DOSAGE AND ADMINISTRATION**)

The sponsor has not submitted data to support a dosage adjustment.

5) **Information for Patients:** ... In order to facilitate delivery to the stomach and possibly minimize gastrointestinal side-effects, patients should take ACTONEL while in an upright position with a full glass (6 to 8 oz) of plain water and should avoid lying down for 30 minutes after taking this medication.

(And also **DOSAGE AND ADMINISTRATION**)

The sponsor has not submitted adequate justification for the change to 10 minutes.

7) **Drug Interactions:** ... Other: No specific drug-drug interaction studies were performed. Although it appears that risedronate itself is not metabolized, its affect on CYP450 pathways has not been elucidated

The sponsor has conducted neither *in vitro* studies to investigate the effect of risedronate on CYP450 activity nor sub-group analyses for the listed drug interactions.

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12/11/97
Carolyn D. Jones, Ph.D.
Robert M. Shore, Pharm.D
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

/S/ /S/ 01/12/98

1/12/98

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 12/15/97

OCPB Briefing: (12/23/97)

Attendees: JonesC, ShoreR, DuttaS, MillerRA, AhnH, LazorJ, ChenME, El-HabetS

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

/S/ 1/12/98

CC: NDA 20-835 (1 copy) HFD-510 (Dutta, Hedin), HFD-340 (Vishwanathan), HFD-870 (Ahn, Jones, Shore, M. Chen), CDR (Murphy).

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APPENDIX
Draft Labeling
Study summaries
Additional Tables

Appendix 1. Draft labeling

9 Page(s) Redacted

DRAFT
LABELING

Appendix 2. Study summaries

Procter & Gamble Pharmaceuticals Risedronate (NE-58095) 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		(For National Authority Use Only)
SYNOPSIS		
BIOAVAILABILITY OF RISEDRONATE (NE-58095) WHEN ADMINISTERED RANDOMLY IN DIFFERENT SOLID DOSAGE FORMS TO NORMAL, HEALTHY MALE VOLUNTEERS		
Protocol No. 91023-995.86.51-0912		
Investigator, Study Center Location:		
Study Period: 89 Days		Clinical Phase: I
First Subject Enrollment Date: 3 November, 1991		Last Subject's Last Observation Date: 30 January, 1992
Objective: To determine the absorption and to compare the biological effects of 30 mg risedronate after oral administration of healthy, male volunteers.		
Study Design: This study was designed as a randomized, complete, three-way crossover design with an 18 day washout between dosing. Subjects received three 10 mg containing 30 mg or one 30 mg		Number of Subjects: Fourteen healthy, adult male volunteers were enrolled in the study. Eleven subjects completed the study.
Study Population: Healthy adult male volunteers:		
Dosage Description: Risedronate 10 mg lot no. CS900048, batch size 30 mg lot no. CS900086, batch size 30 mg lot no. CS900080, batch size		Drug Administration: Three consecutive daily doses, each of 30 mg, by oral administration.
Evaluation of Pharmacokinetics: Blood was collected for 48 h and urine was collected for 72 h after the first dose of each period.		
Evaluation of Pharmacodynamics: Intact parathyroid hormone was measured prior to dosing and at the end of each period. Urinary calcium/creatinine excretion was measured for 72 h after first dose of each period.		
Evaluation of Safety: Safety was evaluated by monitoring adverse events, clinical laboratory measurements, physical examinations and vital signs.		
Subject Accountability/Demographics: The study was conducted in 14 healthy, male volunteers, with 11 subjects completing the study. Subject 09120401 was discontinued due to a positive drug screen for cocaine. Subjects 09120411 and 09120412 chose not to return after the first period. The mean (\pm S.D.) age of all enrolled subjects was 28.6 \pm 5.4 yr and mean (\pm S.D.) weight was 73.1 \pm 7.2 kg		

Results: Least-squares geometric means and 95% confidence intervals are summarized in the following Table. Subjects were inadvertently fed 0.5 h after drug administration rather than 4 h after drug administration on the second and third day of each period; thus, pharmacokinetic and pharmacodynamic results obtained on these days of each period were confounded by a "food effect".

Pharmacokinetic Parameter	Least-Squares Geometric Means ^a (95% Confidence Interval)			P-value for Overall F-test
AUC _t (ng·h/mL)	29.64 (20.52, 42.82)	33.20 (22.98, 47.96)	18.82 (13.03, 27.20)	0.1300
F _{rel} AUC ^b (%)	-	112.0 (62.1, 202.0)	63.5 (35.2, 114.5)	
C _{max} (ng/mL)	8.65 (5.89, 12.72)	10.60 (7.21, 15.58)	5.68 (3.87, 8.35)	0.1463
t _{max} (h)	1.33 (0.71, 1.95)	2.48 (1.87, 3.08)	2.75 (2.12, 3.38)	0.0222
A _{0(0-24 h)} (µg)	85.17 (44.72, 125.63)	134.32 (93.87, 174.78)	83.32 (42.86, 123.79)	0.1697
F _{rel} A _{0(0-24 h)} ^b (%)	-	157.7 (83.8, 222.6)	97.8 (36.5, 168.6)	
CL _R (L/h/kg)	0.0368 (0.0305, 0.0432)	0.0438 (0.0374, 0.0501)	0.0431 (0.0367, 0.0494)	0.3067

^a Arithmetic means are displayed for t_{max}, A_{0(0-24 h)} and CL_R.

^b F_{rel} compares AUC and A₀ of enteric-coated dosage forms to value was calculated for the

thus, no

Data summarized from statistical analyses described in Appendix F, Tables 2-8.

No significant difference in least-squares geometric mean for AUC_t or C_{max} was observed among the three dosage forms. However, as expected a significant formulation effect was observed for t_{max}. The least-squares mean t_{max} for the formulations was later than that observed for the Consistent with AUC, least-squares mean A₀ were also not significantly different among the three dosage forms. No significant differences in the least-squares mean CL_R were observed among dosage forms. No significant formulation-by-time effect was observed in the CL_R.

Administration of food 0.5 h after dosing on Days 2 and 3 of each period severely affected the median absorption of risedronate compared to Day 1 from the enteric-coated dosage forms (A₀ reduced for 122 µg on Day 1 vs. 0.0 µg on days 2 and 3; for tablet, 55 µg on day 1 vs. 31 and 6.0 µg for Days 2 and 3, respectively), with the risedronate absorption from the affected slightly less (A₀ reduced 40%: 89 µg on Day 1 vs. 54 and 52 µg for Days 2 and 3, respectively). These results are consistent with the later t_{max} observed on Day 1 of each period with the enteric-coated dosage forms: e.g., less time for risedronate absorption prior to interaction with food.

Risedronate was well tolerated by all subjects in the study.

Conclusions: C_{max}, AUC_t and A₀ are not significantly different among the dosage forms. As expected, t_{max} is significantly different between the

These results indicate that risedronate delivered via an form provide a similar rate (C_{max}) and extent (AUC_t, A₀) of risedronate absorption, but a delay in the onset of absorption (t_{max}). Administration of food 0.5 h after dosing on Days 2 and 3 of each period resulted in a marked reduction in the median A₀.

Procter & Gamble Pharmaceuticals Risedronate (NE-58095) 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		(For National Authority Use Only)
SYNOPSIS A CROSSOVER STUDY TO COMPARE BIOAVAILABILITY OF RISEDRONATE Protocol No. 92026-995.86.51-0912		
<i>Study Period:</i> 16 Days		<i>Clinical Phase:</i> I
<i>First Subject Enrollment Date:</i> 21 January, 1993		<i>Last Subject's Last Observation Date:</i> 6 February, 1993
<i>Objective:</i> To compare the bioavailability of 1 and 10 mg risedronate		
<i>Study Design:</i> The study design utilized 40 subjects randomly assigned to one of two dose levels, 1 and 10 mg risedronate (20 subjects per dose level). Within each dose level, subjects received risedronate using a randomized, two-way crossover design with either a _____ administered in each period. There was a 14 day washout between each dosing.		<i>Number of Subjects:</i> Forty healthy, male volunteers were enrolled.
<i>Study Population:</i> Healthy adult male volunteers; _____ of age (inclusive).		
<i>Dosage Description:</i> Risedronate 1 mg Lot No. CS900107, Batch Size Risedronate 1 mg t, Lot No. CS900170, Batch Size Risedronate 10 mg ; Lot No. CS900115, Batch Size Risedronate 10 mg Lot No. CS900171, Batch Size		<i>Drug Administration:</i> Single dose (1 or 10 mg) oral administration of two different formulations on two occasions.
<i>Evaluation of Pharmacokinetics:</i> Urine samples were collected for 24 h.		
<i>Evaluation of Safety:</i> Safety was evaluated by monitoring adverse events, clinical laboratory measurements, physical examinations and vital signs.		

Procter & Gamble Pharmaceuticals Risedronate (NE-58095) 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		(For National Authority Use Only)
SYNOPSIS BIOAVAILABILITY OF A SINGLE DOSE OF RISEDRONATE (NE-58095) SOLUTION WHEN ADMINISTERED AT THREE DIFFERENT GASTROINTESTINAL SITES IN NORMAL, HEALTHY MALE VOLUNTEERS 91013-995.86.51-0912		
<i>Study Period:</i> 32 Days	<i>Clinical Phase:</i> I	
<i>First Subject Enrollment Date:</i> 31 July, 1991	<i>Last Subject's Last Observation Date:</i> 31 August, 1991	
<i>Objective:</i> To compare risedronate absorption when administered as a solution to the stomach, duodenum and terminal ileum.		
<i>Study Design:</i> The study was designed as a single dose, 3 period crossover in 9 subjects with a 14 day washout period between dosing. Subjects were fasted overnight and for 4 h after drug administration. Risedronate solution was administered directly into stomach, second part of duodenum, or terminal ileum via naso-enteral tube. Risedronate solution (40 mg in 30 mL water) was administered over 1 minute via the tube.	<i>Number of Subjects:</i> Nine healthy, male subjects were enrolled in the study. Eight subjects completed the study.	
<i>Study Population:</i> Healthy adult male volunteers; _____ of age (inclusive).		
<i>Dosage Description:</i> 40 mg Risedronate solution (1.33 mg/mL) in <i>Drug Substance-Lot No.:</i> RN 71923 (12798-055B)	<i>Drug Administration:</i> Single dose (40 mg) administration via naso-enteral tube into stomach, duodenum or ileum.	
<i>Evaluation of Pharmacokinetics:</i> Blood and urine were collected for 48 h.		
<i>Evaluation of Safety:</i> Safety was evaluated by monitoring adverse events, clinical laboratory measurements, physical examinations and vital signs.		
<i>Subject Accountability/Demographics:</i> The study was initiated utilizing 9 healthy, male subjects, with 8 subjects completing all three test periods. Subject 09120201 chose to withdraw from the study after the first period. The mean (\pm S.D.) age of the subjects was 29.4 ± 7.4 yr and mean (\pm S.D.) body weight was 71.7 ± 4.8 kg.		

Subject Accountability/Demographics: Thirty-nine subjects completed both periods of the study. One subject at the 10 mg dose level, subject 09120832, was discontinued prior to the start of the second period due to a positive drug screen for benzodiazepine metabolites. The mean (\pm S.D.) age of the subjects receiving 1 mg risedronate was 28.4 ± 6.4 yr and mean (\pm S.D.) weight was 75.3 ± 8.6 kg. The mean (\pm S.D.) age of the subjects administered 10 mg risedronate was 25.9 ± 6.1 yr and mean (\pm S.D.) weight was 75.2 ± 8.5 kg.

Results: Least-squares geometric means of cumulative urinary excretion and relative bioavailability are summarized in the following Table.

Dose	Least-Squares Geometric Means of Cumulative Urinary Excretion (μ g) (95% Confidence Interval)		P-value for Treatment Effect	Relative Bioavailability of Film-Coated Tablets Versus Gelatin Capsules
	Gelatin Capsule	Film-Coated Tablet		Ratio of Formulations Expressed as a Percentage (90% Confidence Interval)
1 mg	2.95 (2.16, 4.03)	3.12 (2.28, 4.26)	0.7333	105.84 (79.65, 140.65)
10 mg	30.31 (23.35, 39.36)	31.57 (24.31, 40.99)	0.7813	104.13 (81.11, 133.70)

Data summarized from statistical analyses described in Appendix F, Tables 1.2, 1.3, 2.2 and 2.3.

Cumulative urinary excretion was not significantly different between the two dosage forms at either dose level (1 mg or 10 mg). Although the study was not sized for a bioequivalence comparison, the 90% confidence intervals were only slightly outside the current bioequivalence limits. However, these dosage forms would be considered bioequivalent under proposed guidelines to vary bioequivalence limits based on the intra-subject variability of a drug¹⁴. Based on these proposed guidelines and an intra-subject coefficient of variation for risedronate of 45%, the bioequivalence limits would be

No significant differences in percent of dose excreted in the urine were found between 1 mg and 10 mg gelatin capsules (arithmetic means of 0.355 vs. 0.350%, p-value=0.9390) and between 1 mg film-coated tablet and 10 mg film-coated tablet (arithmetic means of 0.390 vs. 0.369%, p-value=0.7816).

Risedronate was well tolerated by all subjects. The few adverse events reported were all mild in severity and followed to resolution.

Conclusions: The cumulative urinary excretion of risedronate indicates that the extent of risedronate absorption is not statistically different between the two 1 mg dosage forms or between the two 10 mg dosage forms. Although the study is conducted in two parallel groups of subjects, the percent of risedronate dose recovered in urine with the 1 and 10 mg dosage forms is not statistically different. These results indicate dose linearity with these formulations from 1 to 10 mg.

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Procter & Gamble Pharmaceuticals Risedronate (NE-58095) 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		(For National Authority Use Only)
SYNOPSIS BIOAVAILABILITY OF A SINGLE DOSE OF RISEDRONATE SOLUTION (NE-58095) WHEN ADMINISTERED DUODENALLY AT TWO DIFFERENT CONCENTRATIONS AND RATES TO NORMAL, HEALTHY, MALE VOLUNTEERS Protocol No. 91014-995.86.51-0912		
<i>Study Period:</i> 16 Days		<i>Clinical Phase:</i> I
<i>First Subject Enrollment Date:</i> 12 August, 1991		<i>Last Subject's Last Observation Date:</i> 27 August, 1991
<i>Objective:</i> To investigate the extent of absorption of risedronate solution delivered to the second part of duodenum at two rates.		
<i>Study Design:</i> This study was designed as a single dose, 2 period crossover with two weeks washout between dosing. Subjects were fasted overnight and for 4 h after drug administration. Risedronate was administered directly into second part of duodenum via naso-enteral tube. A single 40 mg dose (in 30 or 180 mL of water) of risedronate solution was administered as a rapid (over 1 min) or slow (over 1 h) infusion, respectively, via the tube. This was immediately followed by a rinse with 20 mL deionized water. The tube was removed within 10 min after drug administration.	<i>Number of Subjects:</i> Eight healthy, male volunteers completed the study.	
<i>Study Population:</i> Healthy adult male volunteers; yr of age (inclusive).		
<i>Dosage Description:</i> Risedronate solution (0.22 and 1.33 mg/mL) in <i>Drug Substance Lot No.:</i> RN 71923 (12798-055B)	<i>Drug Administration:</i> Single dose (40 mg) administration via naso-enteral tube into duodenum.	
<i>Evaluation of Pharmacokinetics:</i> Blood and urine were collected for 48 h.		
<i>Evaluation of Safety:</i> Safety was evaluated by monitoring adverse events, clinical laboratory measurements, physical examinations and vital signs.		

Subject Accountability/Demographics: The study was conducted in 8 healthy male volunteers. The mean (\pm S.D.) age was 25.1 ± 4.5 yr and mean (\pm S.D.) weight was 78.4 ± 8.0 kg

Results: Least square geometric means and 95% confidence intervals are summarized in the following Table.

Pharmacokinetic Parameter	Least Square Geometric Means ^a (95% Confidence Interval)		P-value for Overall F-test
	One Minute Infusion at 1.33 mg/mL	One Hour Infusion at 0.22 mg/mL	
AUC _t (ng•h/mL)	43.53 (23.42, 80.91)	39.92 (21.48, 74.20)	0.6609
C _{max} (ng/mL)	14.21 (7.64, 26.42)	10.73 (5.77, 19.95)	0.2467
t _{max} (h)	0.78 (0.21, 1.36)	1.84 (1.27, 2.42)	0.0303
A ₀ (μ g)	235.42 (131.64, 421.02)	192.42 (107.60, 344.12)	0.2230
CL _R (L/h/kg)	0.0670 (0.0556, 0.0785)	0.0594 (0.0479, 0.0709)	0.2107

^a Arithmetic means are displayed for t_{max} and CL_R.

Data summarized from statistical analyses described in Appendix F.

There were no significant carryover effects for any of the pharmacokinetic parameters. No significant differences in least square geometric mean AUC_t and C_{max} were observed following administration of risedronate as a rapid or slow infusion. A significant difference between infusion rates was observed for t_{max}. Consistent with AUC_t, least square A₀ were also not significantly different after dosing as a rapid or slow infusion. No significant differences in the least square geometric mean CL_R were observed between treatment groups. No significant time effect was observed in the CL_R across urine collection intervals.

A total of 3 adverse events were reported in this study, none of which were Serious Adverse Events.

Conclusions: AUC_t and A₀ results indicate the extent of risedronate absorption is not significantly different following a rapid or slow infusion (1 min and 1 h, respectively) of risedronate into the duodenum. Therefore, an immediate-release or sustained-release enteric-coated dosage form should provide similar extent of bioavailability of risedronate. Consistent with a longer infusion, a lower C_{max} and a longer t_{max} were observed.

Publication Reference:

Bekker P, Al-Habet S, Patel V, Wagner D, Dansereau R, Zinny M, Conklin J, and Axelrod D. Pharmacokinetics of urinary excretion of risedronate (NE-58095) following instillation into duodenum at two different concentrations and rates in human. World Conference on Clinical Pharmacology and Therapeutics (Yokohama, Japan, July 26-31, 1992). Abstract # P-305-04 (page 247).

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Evaluation of Safety:

Safety was evaluated by monitoring adverse events throughout the study, routine clinical laboratory measurements, selected clinical laboratory tests, physical examination (including vital signs and oral temperature), and 12-lead ECGs.

Subject Accountability/Demographics:

Thirty-three subjects were enrolled in the study. Mean age and weight at first dose was 33 years, and 75.7 kg. Of the 33 subjects enrolled, 25 completed four periods. No subjects withdrew due to adverse events.

Results

Pharmacokinetic results are summarized in the table below:

Pharmacokinetic Parameters ^a (Estimate of Central Tendency and 95% Confidence Interval)							
Dosage Forms	AUC ^b (ng·h/mL/mg)	C _{max} ^b (ng/mL/mg)	t _{max} (h)	t _{1/2,Z} (h)	A _e (%)	CL _R (L/h/kg)	V _Z (L/kg)
Tablet	0.91 (0.77, 1.07)	0.16 (0.13, 0.19)	1.03 (0.93, 1.14)	218 (202, 236)	0.59 (0.51, 0.68)	0.086 (0.079, 0.093)	4601 (3850, 5499)
Solution	0.87 (0.73, 1.04)	0.14 (0.12, 0.17)	1.23 (1.12, 1.34)	204 (188, 222)	0.56 (0.48, 0.66)	0.087 (0.079, 0.095)	4538 (3752, 5489)
IV	142 (119, 172)	50 (42, 61)	0.99 (0.88, 1.11)	200 (183, 218)	87 (73, 102)	0.080 (0.073, 0.088)	27 (22, 32)
Formulation Comparison ^c	SI	SI	IS	IS	SI	IS	IS

^a AUC is the area under the serum concentration-time profile from time 0 → ∞; C_{max} is the maximum serum concentration; A_e is the cumulative amount of drug excreted in urine normalized for dose and expressed as a percentage; t_{max} is the time that the maximum serum concentration occurs; t_{1/2,Z} is the half-life of the terminal exponential phase; CL_R is the renal clearance; V_Z is the terminal volume of distribution for IV and is uncorrected for bioavailability for Tablet and Solution.

^b Values are dose adjusted.

^c Groups are ordered from smallest to largest mean (geometric or arithmetic) in accordance with the statistical analysis used. Underlined groups indicate no significant group difference.

Pharmacokinetics: Following intravenous administration, CL_R comprised 87% of the CL (0.957 L/h/kg) with only 13% "cleared" via CL_{NR}. The V_{ss} was 6.3 L/kg. The t_{1/2,Z} was 200 h, and not significantly different between intravenous and oral administration.

The absolute bioavailability of risedronate was similar for both the tablet and solution at approximately 0.65%. The F_{rel} was 104% for the tablet compared to the solution, and the 90% CI indicated that the two doses were bioequivalent for the extent of absorption.

C_{max} was not significantly different between the two oral doses, with a ratio of tablet to solution of 110%. Although these doses were not bioequivalent for the rate of absorption (90% CI = 93-130) based on the conventional range, the range is within that proposed for highly variable drugs. The intrasubject CV following intravenous administration was less than 20% for all the parameters. Comparison of intrasubject CV between the two oral doses indicated that the CV for the tablet was generally greater than for the solution (tablet C_{max}, AUC and solution C_{max}, AUC and A_e ~50%). The intersubject CV for the rate (C_{max}) and extent (AUC) of absorption were 9.9 and 15.1% across all three dosage forms.

Safety: There were no serious adverse events or deaths in this study. Twenty-eight subjects (84.8%) reported 132 adverse events. No subjects dropped due to adverse events. The most frequently reported adverse event was headache (22 events in 16 subjects). Twenty-one events were assessed as possibly drug-related, while the remainder, 111 events, were considered to be doubtfully drug-related. Of the 132 adverse events, 117 were mild in severity, 13 were moderate, and 2 were severe. The 2 severe events (toothache and rhus dermatitis) occurred in 2 subjects in the oral tablet formulation group and were considered to be doubtfully drug-related. These two subjects recovered from their adverse experiences.

Conclusions:

The absolute bioavailability of risedronate is <1%. The relative bioavailability of the tablet to the solution is approximately 100%. The intra-subject coefficients of variation were significantly greater for tablet and solution compared to intravenous administration indicating that the variability in the risedronate pharmacokinetics is due to within subject variability in absorption. Overall, risedronate was well tolerated by the study population; there were no serious adverse events or deaths.

Reviewer Comments for Study RAB011594:
• assay acceptable

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Procter & Gamble Pharmaceuticals Tradename of product: Name of active ingredient: 1-hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		For National Authority Use Only
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SYNOPSIS

A DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE I STUDY TO DETERMINE THE SAFETY AND TOLERANCE OF INTRAVENOUS RISEDRONATE (NE-58095) IN HEALTHY ADULT MALE VOLUNTEERS

Study No. 90011-995.86.00-2080

Study Period: 20 days of institutionalization including: a pre-dosing evaluation, followed by the administration of a single dose of study medication, 2 days of observation, and 7 days of dosing. Subjects were followed-up for 7 days after the end of drug administration.	Clinical Phase: Phase I
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First Subject's Enrollment Date: 10 July 1990	Last Subject's Last Observation Date: 28 September 1990
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Objectives:
1) To assess the safety and tolerance of three intravenous doses of risedronate when administered to adult, male volunteers; 2) To investigate the pharmacologic effects following intravenous administration of risedronate at three dose levels; and 3) To study the pharmacokinetics of risedronate when administered intravenously.

Study Design: Double-blind, placebo-controlled, sequential-group, ascending-dose, single-center study. Volunteers received risedronate or placebo as a single dose, then as multiple doses.	Number of Subjects: 19 subjects total; 7 received placebo, and 12 (4 by dose group) received risedronate 0.10, 0.25, or 0.50 mg/day. One subject was discontinued due to a laboratory abnormality and was replaced.
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Criteria for inclusion:
Healthy male volunteers between _____, within 15% of ideal body weight, who had not received bisphosphonates in the past year.

Dosage Description: Risedronate was supplied in ampules containing a 1 mg/mL solution of the active drug (Lot CS900010). 30 mL vials of bacteriostatic saline for injection were used to prepare placebo and final risedronate solutions.	Drug Administration: 4 out of 6 subjects in each dose group were to receive first a single intravenous dose of risedronate 0.10, 0.25, or 0.50 mg/day, then the same dose once a day for 7 consecutive days. The 2 other subjects in each group were to receive intravenous placebo.
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Safety Evaluations:
Subjects were monitored throughout the study. Vital signs and adverse events were recorded daily. Physical examination and ECG recordings were carried out before and after drug administration. Routine hematology, serum chemistry, and urinalysis were performed. Acute phase parameters including body temperature, WBC and lymphocytes, CRP, and Zn were evaluated. Urine was also analyzed for creatinine, calcium, phosphorus, hydroxyproline, and beta-2-microglobulin. Fecal samples were tested for occult blood. The number and consistency of bowel movements were recorded daily. Special safety measurements included iPTH, 25(OH) D₃, 1,25(OH)₂ D₃, serum testosterone, FSH, and LH measurements.

Pharmacologic Evaluation:

Pharmacologic parameters analyzed during the study were serum calcium, phosphate, creatinine, iPTH, 25(OH) D₃, and 1,25(OH)₂ D₃. Urinary calcium/creatinine, hydroxyproline/creatinine, and phosphate/creatinine ratios were also calculated.

Pharmacokinetic Evaluation:

The two pharmacokinetic parameters measured were A₀ (total amount of drug excreted in urine per day) and A'₀ (total amount of drug excreted in urine normalized for dose and expressed as a percentage).

Subject Disposition/Demographics:

Nineteen male subjects (mean 30 years), entered the study. One subject in the placebo group was discontinued due to elevated liver enzymes prior to dosing and was replaced. It was discovered after the conclusion of the study that 3 subjects (2 in the placebo group and 1 in the risedronate 0.50 mg/day group) had been apparently misdosed for one day; none of them experienced any adverse events which could be attributed to misdosing; they were excluded from the safety and pharmacologic analyses.

Results:**Safety:**

Overall, 13 of 16 analyzed subjects reported 53 separate adverse events, none of which were serious. Thirty-four events were clinical adverse experiences and 19 were laboratory abnormalities. The clinical adverse events were coded to the body systems of body-as-a-whole [19 events, including headaches (9 events) and back pain (6 events)], digestive (4 events), skin (3 events), respiratory (3 events), nervous (2 events), or special senses (3 events). There were 17 reports of adverse events in the 0.10 mg/day group, 23 in the 0.25 mg/day group, 3 in the 0.50 mg/day group, and 10 in the placebo group. All adverse events were followed to resolution. There were no significant modifications in renal function or gonadal axis. Acute phase reaction parameters showed no pathogenic effect of intravenous risedronate treatment.

Pharmacologic Results:

As expected, bone metabolism parameters underwent dose-related changes with a decrease in mean serum calcium levels and resulting increases in mean serum iPTH and 1,25(OH)₂ D₃. Decreases in the mean 2-hour urinary calcium/creatinine ratios were observed in all risedronate groups after dosing.

Pharmacokinetics:

A₀ increased in a dose-related manner in subjects administered 0.10, 0.25, and 0.50 mg/day risedronate. The median A'₀ after a single dose ranged from _____ in 24 hours. A comparison of the mean total urinary excretion upon 7 days of dosing versus after a single dose resulted in an accumulation ratio of 1.1, 1.6, and 1.0 for the 0.10, 0.25, and 0.50 mg/day dose groups, respectively.

Conclusions:

Overall, the intravenous administration of risedronate over a _____ range was well tolerated. Most of the adverse events were mild in severity. Dose-dependent decreases in serum calcium and urinary calcium/creatinine were observed, with concomitant increases in iPTH and 1,25-dihydroxy vitamin D₃; these changes were consistent with the expected pharmacologic action of a bisphosphonate. There was no acute phase response to intravenous administration of risedronate. Risedronate exposure (as measured by A₀) increased with increasing intravenous doses. Seven days of daily intravenous dosing resulted in a mean accumulation ratio of _____

Reviewer Comments for Study 90011:

- assay acceptable
- Reviewer's analysis of 'excretion rate vs time plots' resulted in risedronate half-life estimates not included in submission but consistent with rapid distribution from plasma compartment.

Procter & Gamble Pharmaceuticals		(For National Authority Use Only)
Risedronate (NE-58095)		
1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		
<p>SYNOPSIS</p> <p>A STUDY TO EVALUATE THE DURATION OF SAMPLE COLLECTION NECESSARY TO CHARACTERIZE THE PHARMACOKINETICS OF RISEDRONATE AFTER SINGLE DOSE, ORAL ADMINISTRATION OF 30 MG TO NORMAL HEALTHY VOLUNTEERS</p> <p>Protocol No. 1994022</p>		
Study Period: 41 Days		Clinical Phase: I
First Subject Enrollment Date: 17 March 1994		Last Observation Date: 26 April 1994
Objective: To determine the maximum collection period in which blood and urine samples contain quantifiable risedronate concentrations.		
Study Design: Risedronate was orally administered by an open-label, single-dose design to eight subjects.		Number of Subjects: Eight healthy male and female subjects.
Study Population: Healthy, adult male and female volunteers; 10% of ideal body weight. Females must be surgically sterile. within		
Dosage Description: Risedronate 30 mg , Lot No. 72813, Batch Size		Drug Administration: Single dose, oral administration of 30 mg.
Evaluation of Pharmacokinetics: Serum samples were collected for 168 h. Urine samples were collected until two consecutive samples were received with risedronate concentrations below the limit of quantitation.		
Evaluation of Safety: Safety was evaluated by monitoring adverse events, clinical laboratory measurements, physical examinations, ECG and vital signs.		
Subject Accountability/Demographics: The study was conducted in eight healthy male and female volunteers. The only female volunteer, Subject 35238208, withdrew from the study on Day 12 for personal reasons. Two subjects (Subjects 35238203 and 35238204 on Days 33 and 35, respectively) voluntarily withdrew from the study prior to the receipt of two consecutive urine samples with risedronate concentrations below the lower limit of quantitation, because they no longer wanted to continue the study. The mean (\pm S.D.) age for all subjects enrolled was 29.9 ± 6.0 yr and mean (\pm S.D.) weight was 74.4 ± 8.0 kg		

Results: Days on study and pharmacokinetic parameters are summarized in the following Table.

	Time to Last Quantifiable Urine Conc. (h)	Pharmacokinetic Parameters					
		AUC (ng·h/mL)	C _{max} (ng/mL)	t _{max} (h)	A ₀ (µg)	CL _R (L/h/kg)	t _{1/2,z} (h)
Mean	746.7	24.44	4.61	0.80	161.35	0.0898	305.79
SD	165.8	10.29	2.02	0.42	67.00	0.0163	161.12
CV (%)	22.2	42.1	43.8	52.0	41.5	18.1	52.7
Median	769	22.47	4.18	0.59	156.68	0.0865	233.54
Minimum							
Maximum							

SD is the standard deviation, CV is the coefficient of variation.

One subject withdrew from the study on Day 12; this subject was not included in the descriptive statistics.

Two subjects withdrew on Days 33 and 35 prior to the receipt of two consecutive urine samples with risedronate concentrations below the limit of quantitation. Although these subjects did not meet the criteria as a completed subject (receipt of two consecutive urine samples with risedronate concentrations below the limit of quantitation), these subjects were considered completed by the sponsor as data were available for greater than 30 days, and were included in the descriptive statistics. Therefore, the mean and median time to the last quantifiable urine concentration may actually be an underestimation of the true value.

Risedronate was quantifiable in the urine for up to 937 h (39 days), and the median time to the last quantifiable urine concentration was 769 h (32 days).

The median AUC, C_{max}, t_{max} and t_{1/2,z} were 22.47 ng·h/mL, 4.18 ng/mL, 0.59 h, and 234 h. The median A₀ was 157 µg, representing 0.52% of the administered dose. Ninety percent of AUC, or A₀, was achieved by 236 h.

Subjects tolerated risedronate well and there were no significant findings in the safety laboratory determinations or physical examinations.

Conclusions: Risedronate was quantifiable in the urine for up to 937 h (39 days), with a median quantifiable period of 769 h (32 days). Since 90% of the AUC or A₀ was achieved within 236 h (10 days), future bioequivalence studies can be designed with a 10 day sample collection period.

The median t_{1/2,z} observed in this study was 234 h. This is the first t_{1/2,z} for a bisphosphonate that has been determined over a period equivalent to . The observed t_{1/2,z} for risedronate probably reflects the slow release of risedronate from the surface of the bone.

Risedronate was well tolerated by all the subjects.

Reviewer Comments for Study 1994022:

- assay acceptable

APPEARS THIS WAY
ON ORIGINAL

Procter & Gamble Pharmaceuticals		(For National Authority Use Only)
Risedronate (NE-58095) 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		

SYNOPSIS
**STUDY TO EVALUATE CARRYOVER EFFECT AND INTRA-SUBJECT VARIABILITY FOR
RISEDRONATE DOSAGE FORMS**
Protocol No. 92016-995.86.51-0968

<i>Study Period:</i> 31 Days	<i>Clinical Phase:</i> I
<i>First Subject Enrollment Date:</i> 27 July, 1992	<i>Last Subject's Last Observation Date:</i> 26 August, 1992

Objective: To investigate possible carryover effects attributable to a single dose of an risedronate. The study will also provide information on the inter- and intra-subject variability associated with two single doses of a risedronate.

Study Design: The study was designed as a three-period study in 40 healthy male volunteers. Study population was healthy, male subjects, and within 15% of ideal body weight. A two week washout was maintained between the start of each period. The first two periods consisted of drug administration, and collection of pharmacokinetic samples and safety assessments. The third period consisted of the collection of a single blood and urine sample for the measurement of risedronate and safety assessments. No drug was administered during the third period. Subjects were fasted for 10 h prior and for 4 h after drug administration for period 1 and 2. Subjects received a single 10 mg risedronate with 250 mL water.	Number of Subjects: Forty healthy, adult male volunteers were enrolled in the study. Thirty-two subjects completed the study per protocol.
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Study Population: Healthy adult male volunteers;	
Dosage Description: Risedronate 10 mg Drug Product Lot No. CS900070 Batch Size	Drug Administration: Single dose (10 mg) oral administration on two occasions.

Evaluation of Pharmacokinetics: Blood and urine were collected for 48 h.

Results: Least-squares geometric means and 95% confidence intervals are summarized in the following Table.

Pharmacokinetic Parameter ^b	Least-Squares Geometric Means ^a (95% Confidence Interval)		Intra-subject and Total Between Subject CV	
	Period 1	Period 2	Intra-Subject CV (%)	Total Between Subject CV (%)
AUC _t (ng•h/mL)	11.40 (5.60, 23.19)	9.83 (4.83, 20.0)	44.24	59.13
C _{max} (ng/mL)	4.01 (2.08, 7.74)	3.35 (1.74, 6.47)	46.79	55.81
t _{max} (h)	1.17 (0.61, 2.26)	1.10 (0.57, 2.11)	43.60	53.79
A _{e(0-48h)} (µg)	31.50 (15.50, 64.03)	29.66 (14.75, 59.62)	46.84	59.60
CL _{R(0-t)} (L/h/kg)	0.0329 (0.0, 0.12) ^c	0.0349 (0.0, 0.16) ^c	29.16	28.27

^a Arithmetic means are displayed for CL_{R(0-t)}.

^b AUC_t is the area under the serum concentration-time profile from time zero to the time of last quantifiable concentration; C_{max} is the maximum serum concentration; t_{max} is the time that the maximum serum concentration occurs; A_{e(0-48h)} is the cumulative amount of drug excreted in urine from 0 → 48 h; and CL_{R(0-t)} is the renal clearance from 0 → t h.

^c Lower bounds for the confidence interval were truncated to 0.0 since the calculated lower bound was less than zero.

Data summarized from statistical analyses described in Appendix F.

There were no significant carryover effects for any of the pharmacokinetic parameters. Intra-subject and total between subject CV for C_{max} were 47 and 56%, respectively. The intra-subject and total between subject CV for AUC and A_e were approximately 45 and 60%, respectively.

Conclusions: There is no significant carryover effect with risedronate following single dose oral administration of 10 mg with a 2 week washout between dosing. The intra-subject and total between subject variability for rate (C_{max}) and extent (AUC, A_e) of absorption for risedronate are approximately 45 and 60%, respectively, which is similar to, or less than, that reported for other bisphosphonates.

Reviewer Comments for Study 92016:

- assay acceptable
- Serum/Urine collected only for 48 hr post-dose with noncompartmental analysis. Therefore, results are not directly comparable to modeled data (0-inf) from other studies.
- C_{max} in this study is the same as for a 30 mg tablet dose in study RAB - awaiting sponsor response.

APPEARS THIS WAY
ON ORIGINAL

Procter & Gamble Pharmaceuticals Tradename of product: Name of active ingredient: 1-hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt (NE-58095)		For National Authority Use Only
SYNOPSIS DOUBLE-BLIND, PLACEBO-CONTROLLED, RISING, MULTIPLE ORAL DOSE STUDY TO DETERMINE THE SAFETY AND TOLERANCE OF NE-58095 IN ADULT MALE VOLUNTEERS Study No. 88020-903.86.00-2080		
Study Period: 14 days of dosing, preceded by a 3-1/2-day pre-dosing assessment and followed by 3 days of non-treatment follow-up.	Clinical Phase: Phase I	
First Subject's Enrollment Date: 23 June 1988	Last Subject's Last Observation Date: 28 September 1988	
Objectives: 1. To assess the safety and tolerance of 3 oral doses of risedronate (NE-58095) when administered for 14 consecutive days to adult, male volunteers; 2. To investigate the renal pharmacologic effects of subchronic oral administration of risedronate at 3 dose levels; 3. To estimate bioavailability based on urinary excretion of orally administered risedronate.		
Study Design: Double-blind, placebo-controlled, sequential-group, multiple ascending-oral dose, single-center study. Volunteers were institutionalized for 20-1/2 days and received either risedronate or placebo for 14 consecutive days.	Number of Subjects: 19 subjects total; 4 received 5 mg risedronate, 5 received 15 mg risedronate, 4 received 30 mg risedronate, and 6 received placebo. One of the 15 mg subjects was withdrawn for protocol violation and replaced.	
Criteria for Inclusion: Healthy, male volunteers within 15% of ideal body weight, who had not received bisphosphonates in the past year.		
Dosage Description: Risedronate were supplied in 2.5 and 20 mg strength (Lots No.8711-05CS-02 and 8711-05CS-01, respectively). (Lot No.8710-12CS-01).	Drug Administration: 4 out of 6 subjects in each group received one oral dose of either 5, 15, or 30 mg risedronate on 14 consecutive days. The other 2 subjects received placebo.	

Safety Evaluations:

Subjects were monitored throughout the study. Vital signs and adverse events were recorded daily. Physical examination and ECG recordings were carried out before and after drug administration. Routine hematology, serum chemistry, and urinalysis were performed. Urine was also analyzed for creatinine, calcium, phosphorus, and hydroxyproline. Fecal samples were tested for occult blood. The number and consistency of bowel movements were recorded daily. Special safety measurements included intact PTH, 25-hydroxy vitamin D₃, 1,25(OH)₂ D₃, serum testosterone, FSH, and LH measurements.

Renal Pharmacologic Evaluation:

The 3 parameters calculated during the study to assess risedronate pharmacologic action on renal function were creatinine clearance, phosphate clearance, and tubular reabsorption of phosphate.

Pharmacokinetic Evaluation:

Twenty-four hour fractionated collections were made on Days 4, 10, and 16. A₀(0-24 h), cumulative urinary excretion of risedronate for each sample collection day, was calculated. The percent of dose excreted in urine (A'₀) was calculated as the A₀(0-24h) normalized by the daily dose administered.

Subject Disposition/Demographics:

Nineteen male subjects, (mean 27 years), entered the study. There were two withdrawals; one subject in the risedronate 15 mg group (protocol violation) was replaced; the second subject (placebo group) withdrew for personal reasons on Day 15 and was not replaced.

Results:**Safety:**

Overall 3 subjects reported 4 separate adverse events. All adverse events were mild in severity. There were 2 reports of adverse events in the 15 mg risedronate group, 1 in the 5 mg risedronate group, and 1 in the placebo group. One event (abdominal pain, in the risedronate 5 mg group) was considered as possibly drug related by the investigator; the remainder were considered to be doubtfully drug related. All adverse events were followed to resolution.

There were no clinically significant changes in laboratory measurements during the study, except for slight increases of GGTP, SGOT and/or SGPT values in three subjects (one in each risedronate group) that did not require interruption of dosing. The following trends were observed in the bone metabolism parameters after risedronate administration, especially in the two highest dose groups: decrease in mean serum calcium and 24-hour urinary calcium/creatinine, increases in intact PTH and 1,25(OH)₂ D₃. There were no clinically significant changes in the gonadal function tests during the study.

Renal Pharmacologic Evaluation:

Creatinine clearance, phosphate clearance, and tubular reabsorption of phosphate were not affected during dosing or in the follow-up period.

Pharmacokinetics:

A₀(0-24h) increased dose proportionally upon single dose and multiple dose administration of 5, 15 or 30 mg risedronate. The A'₀ for three dose strengths was not statistically different after a single dose or seven daily doses (p = 0.22 and 0.43, respectively). The accumulation ratio ranged

Conclusions:

In this study, the administration of 5 to 30 mg of risedronate daily over a 14-day period was found to be safe and well tolerated. All adverse events were mild in severity and most were considered to be doubtfully drug related. Dose-dependent decreases in serum calcium and urinary calcium/creatinine were observed, with concomitant increases in intact PTH and 1,25(OH)₂ D₃; these changes were consistent with the expected pharmacologic action of a bisphosphonate. Slight increases in GGTP, SGOT and/or SGPT values were observed in 3 subjects, that did not require interruption of dosing. Creatinine clearance, phosphate clearance and tubular reabsorption of phosphate were not affected by drug administration. Risedronate absorption (as measured by A₀) increased dose proportionally from 5 to 30 mg. Median A₀, as compared to the first day of dosing, increased following 13 daily doses indicating accumulation at all dose levels.

Procter & Gamble Pharmaceuticals Trade name of product: Name of active ingredient: 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		(For National Authority Use Only)
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SYNOPSIS

A STUDY TO DETERMINE THE DOSE LINEARITY AND SAFETY OF RISEDRONATE AFTER A SINGLE ORAL DOSE OF 2.5, 5, OR 30 MG TO NORMAL HEALTHY VOLUNTEERS

Study No. RSD005794

of Report: 4 December 1996

Study Period: 29 days	Clinical Phase: Phase I
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First Subject Enrollment Date: 20 July 1994	Last Subject's Last Observation Date: 23 December 1994
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Objectives:

The objectives of this study were: (1) to determine the linearity of risedronate pharmacokinetics after a single dose of 2.5, 5, or 30 mg; and, (2) to assess the safety of risedronate after a single dose of 2.5, 5, or 30 mg in a controlled environment.

Study Design: Double-blind, randomized, parallel design, single-center study.	Number of Subjects: 67 subjects were enrolled in the study and one dropped out. 22 subjects received 2.5 mg risedronate, 22 subjects received 5 mg, and 23 subjects received 30 mg. Six subjects were female (2 per treatment group).
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Study Population:

Healthy male and female volunteers, within 10% of ideal body weight, who had never received bisphosphonates. Females had to be surgically sterile.

Dosage Description: 2.5-mg Batch Size - Lot # 72865 (14241-23B), 5-mg Batch Size - Lot # 72867 (14241-23B), 30-mg Batch Size - Lot # 72813 (14241-22B),	Drug Administration: Single-dose oral administration of 2.5, 5, or 30-mg risedronate tablets.
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**APPEARS THIS WAY
ON ORIGINAL**

Evaluation of Pharmacokinetics:

Pharmacokinetic parameters were determined from serum samples obtained at predose and over 72 hours after dosing, and urine samples collected at pre-dose and over 672 hours post-dose.

Evaluation of Safety:

Safety was evaluated by monitoring adverse events, clinical laboratory measurements (including ionized calcium, PTH, alkaline phosphatase, GGTP, SGOT, SGPT, and creatinine), vital signs, ECGs, and performing physical examinations. Acute phase reaction parameters (including adverse events, oral temperature, zinc, C-reactive protein, total protein + electrophoresis, and WBC + differential) were reviewed before unblinding the study to determine whether analyses of C3 complement and IL-1(β) were necessary.

Subject Accountability/Demographics:

Sixty-seven male and female subjects entered the study. One subject, who received 30 mg of risedronate, dropped out after 15 days on study for personal reasons and was not replaced.

Results:**Pharmacokinetics:**

Analysis of C_{max} , AUC and A'_e indicated single dose oral administration of 2.5 to 30-mg risedronate was dose proportional using a linear contrast model ($p = 0.4603, 0.5477, \text{ and } 0.9688$, respectively). Similarly, t_{max} and CL_R were also not significantly different among the three doses ($p = 0.4710$ and 0.5587 , respectively). However, $t_{1/2,z}$ and V_z/F were significantly different among the three doses ($p < 0.001$ for both parameters). The 2.5 mg $t_{1/2,z}$ was significantly shorter than the 5 and 30 mg $t_{1/2,z}$. For V_z/F , all three dose groups were significantly different, with V_z/F increasing with increasing dose. The statistically significant differences in $t_{1/2,z}$ and V_z/F are probably due to the assay sensitivity restricting the ability to accurately determine the terminal elimination rate constant (λ_z).

Similar to the linear contrast model, analysis of the data by the degree of proportionality model indicated single dose oral administration of 2.5 to 30-mg risedronate was dose proportional.

Safety:

There were no deaths or serious adverse events during the study. Overall, 53 subjects (79.1%) reported 223 adverse events; most of them were mild in severity. There were 26 adverse events of moderate severity. One severe adverse reaction occurred in Subject 45488253 of the 30-mg group, who had intermittent diarrhea during 9 days that the investigator considered to be possibly drug-related. However, the subject recovered and completed the study. The 2 adverse events most frequently reported were headache and abdominal pain. Abdominal pain was associated with viral gastroenteritis in 6 subjects, who had to receive increased fluids. Additionally, 7 subjects in block-2 developed urinary tract symptoms considered to be possibly drug-related by the investigator; however, the occurrence of this event in these subjects and not in others was unexplained. Overall, 8 adverse events were considered to be probably drug-related (back pain [4 events], chest pain [1 event], neck pain [1 event], pain [1 event] and arthralgia [1 event]), 136 possibly drug-related, and 79 doubtfully drug-related. The most common adverse event thought to be possibly drug-related was musculoskeletal pain. There were no clinically significant changes in laboratory measurements during the study. None of the subjects who participated in this study showed a consistent pattern of acute phase response (i.e., elevated body temperature, leukocytes and CRP, and decreased Zn levels).

Conclusions:

Risedronate pharmacokinetics are dose proportional following single dose, oral administration of 2.5 to 30 mg. Risedronate was well tolerated by the subjects. There was no pattern reflecting acute phase response.

Publication:

Ward C, Sacco-Gibson N, Mitchell DY, Kelly S. Single dose risedronate (pyridinyl-bisphosphonate) does not induce acute phase reaction in healthy subjects. J Bone Min Res 1996; 11:S346

Reviewer Comments for Study RSD005794:

- assay acceptable
- 2.5 mg dose resulted in limited detectable risedronate in urine samples.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Procter & Gamble Pharmaceuticals Risedronate (NE-58095) Name of active ingredient: 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		For National Authority Use Only
SYNOPSIS COMPARISON OF THE TIME OF RISEDRONATE ADMINISTRATION IN RELATION TO FOOD AND TIME OF DAY USING FOUR DIFFERENT DOSING REGIMENS AFTER A SINGLE 30 MG ORAL DOSE TO NORMAL HEALTHY VOLUNTEERS Study No. RRF008593		
Study Period: 8 days of institutionalization. Female subjects had to come back on Day 12 for testing.	Clinical Phase: Phase I	
First Subject Enrollment Date: 20 September 1993	Last Subject's Last Observation Date: 31 October 1993	
Objective: To compare the extent and rate of risedronate absorption for four different dosing regimens based on the time of day and the relationship to meals following oral administration of a single 30 mg dose to normal healthy volunteers.		
Study Design: The study was an open-label, single-dose, randomized, parallel study design. Subjects were randomly divided into four groups (Groups I-IV); subjects in each group were then randomly assigned to one of four treatment groups (Groups 1-4): Group 1 was fasted for 10 h prior to drug administration and dosed 4 h prior to meal; Group 2 was fasted for 10 h prior to drug administration and fed a high fat (~55 g) breakfast 1 h after dosing; Group 3 was fasted for 10 h prior to drug administration and fed a high fat (~55 g) breakfast 0.5 h after dosing; and Group 4 was administered drug 2 h after a standard dinner.	Number of Subjects: 127 subjects enrolled in the study.	
Study Population: Healthy male and female subjects, inclusive.		
Dosage Description: Risedronate 10 mg Lot # CS900171; Batch Size	Drug Administration: Single dose oral administration of 3-10 mg tablets.	
Evaluation of Pharmacokinetics: Blood and urine were collected for 168 h after drug administration.		
Evaluation of Safety: Safety was evaluated by monitoring adverse events, clinical laboratory measurements, physical examinations, vital signs and ECGs.		
Subject Accountability/Demographics: A total of 127 subjects were enrolled and 126 completed this study. One subject dropped from the study due to an adverse event. The mean (S.D.) body weights on the day of dosing for each treatment group were 76.7 (10.0), 75.1 (9.9), 76.0 (9.0) and 73.8 (10.4) kg for Groups 1-4, respectively. The mean (S.D.) ages on the day of dosing for each treatment group were 29.9 (5.6), 27.5 (5.0), 28.0 (6.7) and 28.3 (6.3) years for Groups 1-4, respectively. There were no statistically significant differences among treatment groups at screening with respect to body weight, age, height, gender or race.		
Results: Estimates of central tendency and 95% confidence intervals are summarized in the following table.		

Pharmacokinetic Parameters	Estimate of Central Tendency ^{a,b,c} (95% Confidence Interval)				Overall P-value	Multiple Comparisons ^d
	Group 1 Dosed 4 h Before Lunch	Group 2 Dosed 1 h Before Breakfast	Group 3 Dosed 1/2 h Before Breakfast	Group 4 Dosed 2 h After Dinner		
AUC ^a (ng·h/mL)	15.28 (12.74, 18.32)	10.44 (8.69, 12.54)	6.71 (5.60, 8.03)	7.35 (6.16, 8.78)	0.0001	<u>3</u> <u>4</u> 2 1
C _{max} ^a (ng/mL)	3.93 (3.28, 4.71)	3.38 (2.82, 4.06)	2.68 (2.24, 3.20)	0.97 (0.82, 1.16)	0.0001	4 <u>3</u> <u>2</u> 1
t _{max} ^b (h)	0.58 (0.43, 0.74)	0.38 (0.22, 0.53)	0.31 (0.16, 0.47)	1.64 (1.49, 1.79)	0.0001	<u>3</u> <u>2</u> 1 4
t _{1/2,z} ^{c,e} (h)	88.8 (82.2, 121.0)	92.8 (82.9, 107.4)	65.8 (57.7, 90.0)	74.3 (70.5, 116.9)	0.0231	3 <u>4</u> <u>2</u> 1
A _e ^c (μg)	86.7 (76.9, 105.8)	49.6 (46.3, 72.3)	39.2 (31.6, 55.9)	33.8 (30.4, 50.0)	0.0001	<u>4</u> <u>3</u> 2 1

AUC is the area under the serum concentration-time profile from time 0 → ∞; C_{max} is the maximum serum concentration; t_{max} is the time that the maximum serum concentration occurs, corrected for lag time (t_{lag}); t_{1/2,z} is the half-life of the terminal exponential phase; and A_e is the cumulative amount of drug excreted in urine from 0 → ∞.

^a The parameters AUC and C_{max} were analyzed using log-transformed data; therefore, geometric means are reported as the estimate of central tendency.

^b The parameter t_{max} was analyzed using raw data; therefore, arithmetic means are reported as the estimate of central tendency.

^c The parameters t_{1/2,z} and A_e were analyzed nonparametrically using raw data; therefore, medians are reported as the estimate of central tendency.

^d Groups are ordered from smallest to largest using either mean, geometric mean, or mean rank score, in accordance with the statistical analysis used. Underlined treatments indicate no significant difference between treatments.

^e Mean rank scores are the basis for treatment comparisons in the nonparametric analysis. In the case of t_{1/2,z}, the ordering for mean rank scores differs from the ordering for medians.

AUC for subjects dosed 4 h before lunch and 1 h before breakfast (Groups 1 and 2) was significantly larger than for subjects dosed 0.5 h before breakfast and 2 h after dinner (Groups 3 and 4).

Additionally, AUC for subjects dosed 4 h before lunch and 1 h before breakfast (Groups 1 and 2) was significantly different. C_{max} for subjects dosed before a meal (Groups 1-3) was significantly larger than for subjects dosed 2 h after dinner (Group 4). In addition, C_{max} for subjects dosed 4 h before lunch (Group 1) was significantly larger than for subjects dosed 0.5 h before breakfast (Group 3). The t_{max} for risedronate dosed 2 h after dinner (Group 4) was significantly larger than other treatment groups. Additionally, the t_{max} for risedronate dosed 4 h before lunch (Group 1) was significantly larger than for subjects dosed 0.5 and 1 h before breakfast (Groups 2 and 3). The median t_{1/2,z} for subjects dosed 0.5 h before breakfast (Group 3) was significantly shorter than those subjects dosed 1 or 4 h before a meal (Groups 2 and 1). This difference in t_{1/2,z} is probably due to the inability to quantitate serum or urine concentrations over an adequate time period to accurately estimate t_{1/2,z} among the groups. Consistent with AUC, subjects dosed 4 h before lunch and 1 h before breakfast (Groups 1 and 2) had significantly greater A_e than subjects dosed 0.5 h before breakfast and 2 h after dinner (Groups 3 and 4).

Only minor symptomatic complaints and unrelated laboratory abnormalities were observed in the subjects of this study. However, one subject dropped from the study due to an adverse event. None of the adverse events was accompanied by clinically significant laboratory abnormalities. There were no serious clinical adverse events.

Conclusions: Phase II studies were conducted with risedronate administered 2 h after a meal (generally dinner) and phase III studies are being conducted with risedronate administration 0.5-1 h prior to breakfast. The extent of absorption (AUC, A_e) was not statistically significantly different between dosing 2 h after dinner and 0.5 h before breakfast; however, the rate of absorption (C_{max}) was 2.5-fold greater when risedronate was administered before breakfast. The rate and extent of absorption were 3.3- and 1.4-fold greater, respectively, when risedronate was administered 1 h before breakfast as compared to 2 h after dinner. These results indicate that the phase III dosing regimen should provide extent of absorption equal to, or greater than, the phase II dosing regimen, but a significantly greater rate of absorption.

Publication: Mitchell DY, Vandenuweland FA, Heise MA, et al. Effect of food on risedronate pharmacokinetics in healthy volunteers. Pharm. Res. 1994, 11:S-370.

Reviewer Comments for Study RRF008593:

- assay acceptable.

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Procter & Gamble Pharmaceuticals Trade name of product: Name of active ingredient: 1-Hydroxy-2-(3-pyridinyl) ethylidene bisphosphonic acid monosodium salt		For National Authority Use Only
SYNOPSIS THE EFFECTS OF RENAL IMPAIRMENT AND DIALYSIS ON RISEDRONATE PHARMACOKINETICS AFTER SINGLE DOSE, ORAL ADMINISTRATION OF 30 MG Study No. RRI013294		
Study Period: 47 Days	Clinical Phase: Phase I	
First Subject's Enrollment Date: 01 May 1995	Last Subject's Last Observation Date: 24 April 1996	
Objective: The objective of this study was to determine the influence of renal impairment and dialysis on risedronate pharmacokinetics. Subjects with ongoing dialysis were excluded from the study per amendment.		
Study Design: Single center study with an open-label, single-dose, balanced parallel study design in adult, male and female subjects with varying degrees of renal impairment.	Number of Subjects: 21 subjects	
Study Population: Male and female subjects, at least 18 years of age, with varying degrees of renal impairment (CL _{CR} =10-120 mL/min), within 30% of ideal body weight, and who had not received bisphosphonates in the past year. Females had to be surgically sterile.		
Dosage Description: Risedronate 30-mg- Lot No. 72813, Batch Size	Drug Administration: 30-mg single oral dose administration.	

Evaluation of Pharmacokinetics:

Pharmacokinetic parameters were determined from serum and urine samples obtained over 72 hours, and urine samples from timed 8-hour collections obtained between 96 and 120 hours post-dose, then twice a week over 6 weeks.

Evaluation of Safety:

Subjects were monitored throughout the study. Adverse events were recorded at every visit. Vital signs were recorded and physical examination and ECGs were performed. Routine serum chemistry, hematology, pregnancy test if applicable, drug screen, and urinalysis were carried out. Blood samples were also collected for ionized calcium and h(1-84) PTH.

Subject Accountability/Demographics:

21 male and female subjects entered and completed the study. Subjects were divided into 4 groups based on the average of two screening creatinine clearances (CL_{CR}). Groups were as follows: 6 subjects in Group I ($CL_{CR} > 80$ mL/min); 6 subjects in Group II (60-80 mL/min); 6 subjects in Group III (30-60 mL/min); and 3 subjects in Group IV ($CL_{CR} < 30$ mL/min).

Results:**Pharmacokinetics:**

Regression analysis using CL_{CR} as an independent variable for the pharmacokinetic parameters indicated that CL_R and V_z/F could be fitted to a simple linear regression model ($p = 0.0001$ and 0.0039 , respectively). A 77% and 74% decrease in predicted CL_R and V_z/F , respectively, were observed when CL_{CR}

Consistent with CL_R , a trend toward a lower CL_O was observed with a 44% decrease in predicted CL_O . No other pharmacokinetic parameters were significantly related to CL_{CR} .

Regression analysis using iohexol clearance (CL_{IO}) as a predictor of renal function produced similar results to those found with CL_{CR} . CL_R and V_z/F were statistically significant with CL_{IO} ($p = 0.0001$ and 0.0011 , respectively). Regression of CL_O on CL_{IO} was not statistically significant. These results were not unexpected as CL_{IO} and CL_{CR} are highly correlated ($r = 0.97$, $p = 0.0001$).

Safety:

Overall 11 subjects reported 22 adverse events, of which 20 were considered to be doubtfully drug-related. The two events that were considered possibly related to drug were single episodes of headache. There were no drop-outs due to an adverse event. One subject in Group IV had a serious adverse event (left hip dislocation) that the investigator considered to be doubtfully drug-related. The most frequently reported adverse event was headache. There were no clinically significant changes in laboratory measurements, vital signs, and electrocardiograms during the study period.

Conclusions:

CL_R was significantly reduced with a decrease in renal function (CL_{CR}). Consistent with CL_R , there was a 44% reduction in CL_O . These results suggest that only patients with severe renal impairment ($CL_{CR} < 20$ mL/min) could require a dosage adjustment (either decrease the risedronate dose by 50% or double the interval between doses). Risedronate was well tolerated by the study population.

Name of Sponsor/Company: Procter & Gamble Pharmaceuticals Name of Finished Product:	Location of Full Report in the Submission <V1.063/p418>	(For National Authority Use Only)
Name of Active Ingredient: risedronate sodium		

Pharmacokinetics - Special Study

Study Title: Plasma Protein Binding of NE-58095 in the Rat, Dog and Human

Report Date: 27-Sep-93 **Study No.:** 995.69.00-AF (43965) **Study Period:** Initiated Mar-92

Principle of Test: Freshly isolated plasma was combined with a constant amount of ¹⁴C-risedronate and different amounts of unlabeled risedronate to give drug concentrations over a range of concentrations. Following incubation at 37°C for 3 hr, aliquots of drug-containing plasma were centrifuged. Concentrations of radioactivity in the sample and ultrafiltrate were determined.

Test Substance: risedronate (in distilled water) **Lot No.:** 13127-061A (labeled) 11661-JKL-11B (unlabeled)

Summary of Percentage of Risedronate Human Plasma Protein Binding

Concentration (µg/mL)	% Risedronate Bound
0.01	93.7 ± 0.58
0.05	90.3 ± 3.01
0.10	ND
0.25	95.0 ± 0.61
0.75	ND
1.0	83.6 ± 4.46
10.0	67.6 ± 4.31

Values are mean ± standard deviation (n=3-7); ND=not determined

Conclusion: Risedronate is highly bound to plasma proteins in humans. Protein binding of risedronate in humans is but progressively decreases at drug levels above 0.25 µg/mL.

Study conducted by the applicant: Yes No

If "no", indicate the name and address of the institute that conducted the study:

Name:
Address:

Study in compliance with GLP: Yes No

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Appendix 3. Assay performance

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