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APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION OF NDA

Application number:	22-560
Supporting document/s:	1
Applicant's letter date:	September 24, 2009
CDER stamp date:	September 24, 2009
Product:	Risedronate-sodium delayed release tablets (TRADENAME)
Indication:	Treatment (b) (4) of PMO. (b) (4)
Applicant:	Warner Chilcott Co LLC
Review Division:	DRUP, HFD-580
Reviewer:	Gemma Kuijpers
Supervisor/Team Leader:	Lynnda Reid
Division Director:	Scott Monroe
Project Manager:	Karl Stiller

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability
From Pharmacology/Toxicology perspective, this NDA can be approved.

1.1.2 Additional Non Clinical Recommendations
No additional nonclinical studies are needed.

1.1.3 Labeling
The labeling proposed for risedronate sodium plus EDTA delayed release tablets included several sections taken from the PLR labeling for Actonel, approved on July 24, 2009 (NDA 20-835/S-035). Actonel approved indications are postmenopausal osteoporosis (5 mg/day, 35 mg/week, 2x75mg or 150 mg/month), osteoporosis in men (35 mg/week), glucocorticoid-induced osteoporosis (5 mg/day) and Paget's disease (30 mg/day). The proposed labeling also includes data from clinical and clinical pharmacology studies conducted with the (b) (4) product.

The following sections of the label contain nonclinical data: Sections 8.1 Pregnancy; Section 8.3 Nursing Mothers; Section 10 Overdosage; Section 12.1 Mechanism of Action; Section 12.3 Pharmacokinetics/Distribution; Section 13.1 Nonclinical Toxicology - Carcinogenesis, Mutagenesis, Impairment of Fertility; and Section 13.2 Animal Toxicology and/or Pharmacology. (b) (4) . The doses used in nonclinical studies described in the Pregnancy, Overdosage, Carcinogenesis and Impairment of Fertility sections are expressed as multiples of the highest approved daily dose of 30 mg/day for Paget's disease (mg/m2 basis). The doses used in nonclinical bone quality studies described in the Animal Toxicology and/or Pharmacology section are expressed as multiples of the approved 5 mg daily dose (mg/m2 basis).

Although Paget's disease is not an indication for this product the multiples based on the 30 mg/day dose for this indication can be maintained since this provides a conservative evaluation of the nonclinical toxicology data. Multiples based on the 5 mg daily dose for the nonclinical bone pharmacology studies (Section 13.2) can also be maintained. Multiples based on mg/m^2 dose comparison are conservative because they have been found to be smaller than multiples based on AUC comparison when available. Minor changes recommended for the nonclinical sections (Sections 8.1, 10, 13.1, 13.2) are attached to this review (APPENDIX III). No other labeling changes are needed based on the nonclinical data submitted to NDA 22-560.

1.2 Brief Discussion of Nonclinical Findings

To support the use of the delayed-release (DR) tablet containing 35 mg risedronate and (b) (4) EDTA, the sponsor conducted a 13-week dog study with weekly doses of risedronate (8 or 16 mg/kg) with or without EDTA (2.5 or 12.5 mg/kg). The 8 mg/kg risedronate dose yielded a 36-fold multiple of human exposure (AUC) and the 16 mg/kg dose a 430-fold multiple. The low dose of EDTA is equivalent to a 80 mg dose in humans, and the high dose to a 400 mg dose in humans (on mg/m^2 basis).

Risedronate effects at both 8 and 16 mg/kg doses included decreases in body weight and food consumption (in males), persistence/hypertrophy of primary spongiosa (pharmacologic effect), serum Ca and P decreases, ALT and AST increases, kidney weight increase, and histopathological changes in kidney (de/regeneration, cell enlargement, inflammation), liver (atrophy) and stomach (cell necrosis, regenerative hyperplasia, inflammation). At 16 mg/kg, additional effects included hematology and clinical chemistry changes (RBC decrease, increase in globulin, decrease in albumin, increase in bile acid), liver effects (vacuolation and glycogen decrease), stomach mineralization, and changes in lymph nodes, abdominal vein, testis and aorta. The effects have been observed previously in risedronate oral toxicity studies in the dog.

The main effect of EDTA was to increase risedronate exposure and exacerbate risedronate toxicities, including systemic and local gastric toxicity. EDTA alone had no effects on any pharmacologic parameter, including bone morphology, and the addition of EDTA to risedronate did not cause any new toxicities beyond those already observed in the risedronate-only groups. The enhancement of toxicity, as well the increase in risedronate exposure by EDTA, was most prominent at the low 8 mg/kg dose of risedronate. The exacerbation of risedronate-induced toxicities was seen with the 12.5 mg/kg dose of EDTA only. The increase in local gastric toxicity was seen only in females. The NOAEL for risedronate was less than 8mg/kg (<36x human AUC) and the NOAEL for the EDTA-induced exacerbation of local and systemic toxicity was 2.5 mg/kg (0.8x human (b) (4) dose). The data suggest that EDTA in the DR tablet may enhance risedronate absorption and risedronate-related gastrointestinal and systemic toxicities.

Long term animal toxicity studies with oral EDTA have shown low toxicity and suggest no issues with a weekly dose of (b) (4) The NOAEL in a 2-year dietary rat study was used to define an acceptable daily intake (ADI) of 150 mg per day (JECFA, 1974). The addition of a weekly dose of (b) (4) to the maximum estimated intake of approximately 650 mg per week does not raise significant safety concerns. The (b) (4) EDTA dose in the DR tablet is unlikely to have a significant effect on bone and mineral metabolism and the EDTA-risedronate combination is unlikely to have adverse effects on bone. Nonclinical bone quality studies with the risedronate-EDTA combination have not been conducted since there is no significant cause for concern.

In the pivotal Phase 3 study, BMD increase and bone turnover suppression were observed that were slightly larger with the 35mg DR than with the 5mg IR product. Also, in clinical studies with the DR formulation an increase in urine Ae (amount excreted) of risedronate of 2x-4x, probably reflecting an increase in absorption and systemic

exposure, has been observed. Based on adequate safety margins derived from nonclinical studies, such an increase in risedronate exposure is unlikely to cause an impairment of bone mineralization or an overt deterioration of bone quality. However, it may be associated with an increased risk for drug-related adverse events in all organ systems including the skeleton.

Conclusions

- Based on toxicology data obtained with EDTA alone, the (b) (4) Na_2EDTA dose in the DR product is acceptable.
- Based on data from a 13-week dog study, the EDTA in the DR tablet may enhance risedronate absorption and risedronate-related systemic toxicities. The EDTA in the DR tablet may also exacerbate risedronate-related GI toxicity.
- The EDTA in the DR tablet may increase paracellular permeability to risedronate as well as co-administered drugs. This issue is addressed by the Clinical Pharmacology Reviewer.
- Increased risedronate exposure with the DR product is unlikely to cause impairment of bone mineralization or overt deterioration of bone quality.
- Increased risedronate exposure with the DR product may lead to a higher risk for drug-related adverse events including skeletal events.

2 Drug Information

2.1 Drug

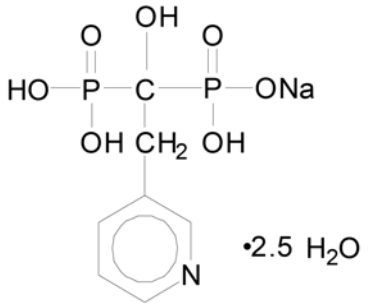
2.1.1 CAS Registry Number
105462-24-6

2.1.2 Generic Name
Risedronate sodium

2.1.3 Code Name
NE-58095

2.1.4 Chemical Name
[1-hydroxy-2-(3-pyridinyl) ethylidene] bis[phosphonic acid]monosodium salt

2.1.5 Molecular Formula/Molecular Weight
Molecular Formula: $C_7H_{10}NO_7P_2Na \cdot 2.5H_2O$
Molecular Weight: 350.13 (hemi-pentahydrate)

2.1.6 Structure


2.1.7 Pharmacologic class
Risedronate sodium (NE-58095): Pyridinyl Bisphosphonate
EDTA (excipient): (b) (4) chelator

2.2 Relevant IND/s, NDA/s, and DMF/s

IND 74,086 Risedronate + EDTA (delayed release formulation)
IND 31,029 Risedronate
NDA 20-835 Risedronate (Actonel)

2.3 Clinical Formulation

2.3.1 Drug Substance

The drug substance (risedronate sodium) in the delayed release enteric-coated tablet is the same as the drug substance in the approved immediate release film-coated tablets (Actonel®). (b) (4)

Specifications
NOTE: The qualification threshold for impurities in the drug substance (b) (4) for doses ≤ 2 g/day) has not been exceeded.

Test	Acceptance Criteria	Procedure
Description	A white to off-white powder	Visual
Identity: Risedronate sodium	The infrared spectra of the sample match reference standard spectra similarly obtained	Infrared
(b) (4)		
Heavy metals	(b) (4)	(b) (4)
Residual solvent: (b) (4)	(b) (4) maximum	(b) (4)
Assay: Sodium	7.2-8.0% AB	Ion chromatography
Assay: Risedronate sodium Impurities: Single unknown impurity*	(b) (4) (b) (4) maximum	HPLC for assay of risedronate sodium and related impurities
Impurities: (b) (4) Single unknown impurity*	(b) (4) maximum maximum	(b) (4)
Total impurities	(b) (4) maximum	(b) (4)
Particle Size	D[v,0.5]: D[v,0.9]: maximum (b) (4)	

AB: Anhydrous basis
* Examination for unknown impurities is done (b) (4)

2.3.1 Drug Product

Risedronate Sodium Delayed-Release Tablet, 35 mg

Ingredient	Function	Unit Quantity (mg/tablet)	% w/w
(b) (4) Risedronate sodium	Active	35.0 a, b	10.00
ProSolv SMCC 90	(b) (4)		
Edetate disodium, c USP			
Sodium starch glycolate, NF			
Stearic acid, NF			
Magnesium stearate, NF			
(b) (4)			
(b) (4) Methacrylic acid copolymer (b) (4) NF (b) (4) (b) (4)			
Triethyl citrate, NF			
Talc, USP			
Ferric oxide, NF, yellow			
Simethicone, USP			
Polysorbate 80, NF			
(b) (4)			
Target Total Enteric Coated Tablet Weight		350 mg	100.0

a Equivalent to 32.48 mg risedronic acid.
b (b) (4)
c Edetate disodium, USP (b) (4)
d (b) (4)
e (b) (4)
f

Specifications
NOTE: There is no change in the impurity profile information/data filed in previous submissions for the approved immediate release dosage strengths. The qualification threshold for degradation products in drug products ((b) (4) for daily doses of 10-100 mg) is not exceeded for this product.

Test	Acceptance Criteria	Procedure
Description [a]	Yellow, oval shaped, coated tablet, engraved with appropriate identification on one side	Visual
Identification [b] Risedronate sodium	The spectrum of the sample matches a reference spectrum similarly obtained.	Raman or Infrared
Content Uniformity [b]	Meets USP <905> requirements for Uniformity of Dosage Units Acceptance value (b) (4)	(b) (4)
Assay [a] Risedronate sodium	Label: 35 mg/tablet Tolerance: 31.5-38.5 mg/tablet 90.0 – 110.0% label	HPLC Alternate - Automated HPLC
Dissolution [a] Acid Stage: (b) (4) in (b) (4) Buffer Stage: (b) (4) (b) (4)	No individual value exceeds (b) (4) dissolved. Meets USP ⟨711⟩ acceptance table criteria for delayed-release dosage forms. Not less than (b) (4) of the labeled amount is dissolved in (b) (4) Meets USP ⟨711⟩ acceptance table criteria for delayed-release dosage forms.	(b) (4)
Degradation Products [c] Single Unknown Total	(b) (4) maximum maximum	

a Performed both at time of manufacture and for stability evaluation
b Performed at time of manufacture only
c Performed for stability evaluation only

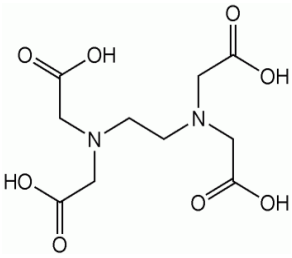
2.3.3 Drug Formulation

Delayed-release, enteric-coated tablet containing 35 mg of anhydrous risedronate sodium, equivalent to 32.48 mg of risedronic acid.

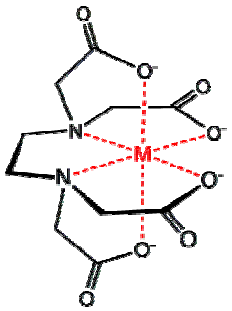
2.3.4 Novel Excipients

The product contains EDTA-disodium (b) (4), and several inactive ingredients. EDTA is not present as an excipient in approved oral drug products. EDTA (as Na_2EDTA and $CaNa_2EDTA$) is widely used and FDA-approved as a direct food additive as a preservative, processing aid, stabilizer and/or chelating agent (e.g. in canned soft drinks, canned vegetables, margarine, pickles) at 25-800ppm ($CaNa_2EDTA$) or 36-500ppm (Na_2EDTA). EDTA and its salts are also used as chelating agents in cosmetic preparations at concentrations < 2%. As EDTA-calcium-disodium (Calcium Disodium Versenate) it is approved for the treatment of heavy metal poisoning, at an IV or IM dose of 1000 mg/m2/day (ca. 2500 mg/day for an adult). EDTA-disodium (Endrate) is approved for emergency treatment of hypercalcemia and treatment of digitalis-induced arrhythmia, with IV doses of 50 mg/kg/day, up to a maximum of 3 grams/day, infused over ≥3h, daily for 5 days. At high doses, reported

side effects of EDTA include low blood sugar, hypocalcemia, skin reaction, headache, nausea, hypotension, kidney failure, cardiac arrest, respiratory arrest, seizures, and death. EDTA is also used in unapproved “chelation therapy” at high iv or daily doses, e.g. 2-3 gram up to 3x per week for 10-12 weeks (IV), or 1000-2000 mg/day for 3 weeks (oral). The benefits of this type of therapy for atherosclerosis or (cardio)vascular disease are highly controversial and its safety is questionable.



EDTA (Mw 292.2)



EDTA-metal (M) chelate

Mw Na_2EDTA dihydrate = 372

Mw risedronate = 350

Molar ratio in tablet risedronate: EDTA = (b) (4)

2.3.5 Impurities/Degradants of Concern

None

2.4 Proposed Indication and Dosing Regimen

Indications: Treatment (b) (4) of postmenopausal osteoporosis (b) (4)

Dosing Regimen: The 35 mg delayed release tablet is to be taken once-a-week, in the morning (b) (4) To facilitate delivery to the stomach the tablet should be swallowed whole while the patient is in an upright position and with at least 4 oz. of water. Patients should not lie down for 30 minutes after taking the medication.

2.5 Regulatory Background

Risedronate sodium (Actonel) as an immediate-release formulation and is currently approved for:

- postmenopausal osteoporosis (5 mg/day, 35 mg/week, 75 mg/2 consecutive days/month, 150 mg/month)
- glucocorticoid-induced osteoporosis (5 mg/day)

- Paget's disease of bone (30 mg/day)
- treatment of osteoporosis in men (35 mg/week).

Data can be referenced in NDA #20-835 (30 mg/day), S001-S004 (5 mg/day), S008-S009 (35 mg/week), S025 (75 mg/2 days/month), S022 (35 mg/week), and S030 (150 mg/month).

The pre-IND meeting for IND 74,086 was held with DMEP on February 15, 2006. IND 74,086 was submitted to DMEP on June 13, 2006. The EOP2 meeting with DMEP was on June 28, 2007. The Pre-NDA meeting was held with DRUP on April 21, 2009.

The sponsor was notified in May 2006 that EDTA (b) (4) USP was considered an excipient and not an active ingredient.

During the pre-IND meeting the Division (DMEP) stated that nonclinical studies with the new formulation were not required to support the Phase 2/3 studies or the NDA. However, in the EOP2 meeting the Division recommended that the Sponsor conduct repeat dose toxicity studies with risedronate and EDTA to assess lower GI toxicity. DMEP provided feedback on the initial protocol for a 13-week dog study on January 9, 2008 to include a low and high dose of EDTA.

2.6 Product development

(b) (4)

2.7 Clinical Program

Clinical studies conducted with immediate release (IR) and delayed release (DR) formulations

- three Phase 1 single dose absorption studies (35 mg risedronate formulations)
- two Phase 1 single dose cross-over bioavailability (BA) studies (20 and 35 mg formulations)
- one BE and BA study with the Phase 3 and commercial formulation (Study 2008119) (35 mg DR tablets)
- a PK and tolerability study (Study 2008076) (75-150 mg IR or DR)
- two extrinsic factor PK studies (35 mg DR)
- a Phase 2 PK/PD study (Study 2005107) (35 mg IR, 35 mg DR, 50 mg DR)
- a Phase 3 noninferiority PD study (Study 2007008) with 5 mg daily before breakfast (IRBB), 35 mg weekly immediately following breakfast (DRFB), and 35 mg weekly 30 minutes before breakfast (DRBB)

Other studies have been conducted with risedronate doses up to 150 mg (approved dose for once monthly regimen).

PK data on amount of risedronate excreted in the urine (Ae, in µg) are available from the Phase 1 absorption studies and the Phase 2 dose finding Study 2005107. Data on Cmax and AUC were obtained only in the BE/BA Study 2008119. Data from this study

with the 35 mg DR formulation showed mean Cmax (35 mg DR) = 14.1 ng/mL and mean AUC = 34 ngxh/mL.

The Phase 2 dose finding Study 2005107 showed efficacy reflected by reductions in serum resorption and formation markers CTx, NTX and BSAP. This effect was more pronounced with the 35 mg and 50 mg DR tablets than the approved 35 mg IR tablet. Absorption reflected by $Ae_{0\text{-}48h}$ was on average 2x-3x higher in the 35 mg DR group than the 35 mg IR group. However, some subjects may be poor absorbers. Other Phase 1 studies have shown that absorption of the 35 mg DR tablet is increased up to 4x compared to the 35 mg approved IR tablet. The increased absorption may reflect an increase in systemic exposure.

Phase 3 Study 2007008 showed efficacy in all three treatment groups (5 mg IRBB, 35 mg DRFB, 35 mg DRBB), as reflected by an increase in % change from baseline of LS-BMD and a decrease in bone markers. The 35 mg DR dose was non-inferior to the 5 mg IRBB dose. PK data were not collected in this Phase 3 trial. Safety data suggest an increase in adverse events with the 35 mg DR formulation, particularly GI events. PTH appeared to be elevated in more subjects treated with the 35 mg DR tablets. This Phase 3 study is a 2-year trial with 1-year data submitted. Histomorphometry data will be collected at the 2-year time point.

2.7 Toxicology Program

The pharmacology and toxicology of risedronate have been evaluated in nonclinical studies with different dosing regimens, including PD, PK, single and repeat-dose toxicity studies, reproductive toxicity, genotoxicity and carcinogenicity studies. In long term (≥26 week) studies with daily dosing in rats and dogs, target organs of toxicity included liver, kidney, stomach, and lung in both rats and dogs, and testes, esophagus, intestine, pancreas, and lymph nodes only in dogs. The no observed adverse effect dose level (NOAEL) was 8 mg/kg/day in rats and 4 mg/kg/day in dogs (≥ 13 wks). To support clinical monthly dosing, up to 13-month dog studies with monthly dosing were conducted (0, 16, 32, 64 mg/kg). Toxicities were observed in the stomach, esophagus, liver, and kidney. The NOAEL was <16 mg/kg for local (stomach) toxicity and 16 mg/kg for systemic (kidney, liver) toxicities. Exposure (AUC) multiples at the dog NOAEL were at least 2-fold lower for monthly compared to daily dosing regimens for local (stomach) and systemic (liver, kidney) toxicities. Risedronate was not genotoxic, not teratogenic (rat, rabbit) and not carcinogenic (32 mg/kg/day in mice, 24 mg/kg/day in rats).

3 Studies Submitted

3.1 Studies Reviewed

Dog study

3.2 Studies Not Reviewed

(b) (4)

[redacted]

3.3 Previous Reviews Referenced

IND 74,086, original IND and amendments
NDA 20-835, original NDA and supplements (S-025 2x75 mg once monthly; S-030 150 mg once monthly)

4 Pharmacology

4.1 Primary Pharmacology

Risedronate sodium has a high affinity for hydroxyapatite crystals in bone and is a potent inhibitor of osteoclasts. It reduces osteoclast activity and induces apoptosis by inhibiting enzymes of the mevalonate pathway with subsequent disruption of intracellular signaling.

No new data are available.

4.2 Secondary Pharmacology

No new data are available.

4.3 Safety Pharmacology

No new data are available.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The effect of EDTA on the PK of risedronate (with or without food) has not been addressed in separate nonclinical PK studies. However, data on risedronate PK in absence and presence of EDTA were obtained in the 13-week dog toxicity study.

5.2 Toxicokinetics

TK data were collected in the 13-week dog study with risedronate (8 and 16 mg/kg) in the absence or presence of 2.5 and 12.5 mg EDTA. The dogs in that study were dosed with gelatin capsules in the fasting state and food was given ≥2h after dosing. The TK data showed that exposure to risedronate (Cmax and AUC) was enhanced by EDTA at both EDTA doses especially at the low 8 mg/kg risedronate dose.

6 General Toxicology

6.1 Single-Dose Toxicity

No new data available.

6.2 Repeat-Dose Toxicity

Study title: 13-Week Oral Capsule Toxicity and Toxicokinetic Study with NE-58095 and EDTA in Dogs

Study no.:	995.09-63236 (Sponsor) 6114-579 (b) (4)
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Febr 7, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RIS: 0000415155 EDTA: 601H6106

Key Study Findings

- A 13-week toxicity study was conducted in beagle dogs with weekly oral doses of risedronate (8 or 16 mg/kg) with or without EDTA (2.5, 12.5 mg/kg).
- Risedornate effects at both 8 and 16 mg/kg included bone hypertrophy, decrease in food consumption and body weight/gain in males, serum Ca and P decreases, ALT and AST increases, kidney weight increase, and histopathological changes in the kidney, liver and stomach. The stomach effect (necrosis, inflammation, hyperplasia) was probably a local toxicity effect.

- Risedronate effects at 16 mg/kg included hematology and chemistry changes, additional histologic changes in liver, stomach, lymph nodes, abdominal vein, testis, and aorta.
- EDTA alone had no effects. EDTA at 12.5 mg/kg exacerbated risedronate's systemic toxicities and the pharmacologic effect on bone. EDTA (12.5 mg/kg) also enhanced stomach irritation in females treated with 8 mg/kg.
- Risedronate exposure (Cmax, AUC) was increased >>2x from 8 to 16 mg/kg. Exposure was also increased by both doses of EDTA with the most pronounced effect in the 8 mg/kg groups.
- Exposure multiples for risedronate, based on comparison to human AUC with the 35 mg DR tablet (AUC = 34 ngxh/mL), were 36x (at 8 mg/kg) and 429x (at 16 mg/kg).
- NOAEL for risedronate (systemic and local gastric toxicity) was ≤ 8 mg/kg, i.e., **≤36x** the human AUC.
- NOAEL for EDTA (systemic and local toxicity enhancement) was 2.5 mg/kg, or **0.8x** human dose of EDTA (mg/m^2 basis).

Methods

Doses:	0, 8, 16 mg/kg (RIS); 0, 2.5, 12.5 mg/kg (EDTA)
Frequency of dosing:	Once weekly
Route of administration:	Oral
Dose volume:	N/A
Formulation/Vehicle:	Gelatin capsule (size no. 12)
Species/Strain:	Beagle dogs
Number/Sex/Group:	6
Age:	171-209 days (6-7 months)
Weight:	7.1-9.3 kg males; 5.1-7.3 kg females
Unique study design:	
Deviation from study protocol:	

Group	No. of Animals Male	Female	Dose Level NE-58095 (mg/kg/dose)	Dose Level EDTA (mg/kg/dose)
1 (Control)[a]	6	6	0	0
2 (Low)	6	6	8	0
3 (High)	6	6	16	0
4 (EDTA Control)	6	6	0	2.5
5 (EDTA Low)	6	6	8	2.5
6 (EDTA High)	6	6	16	2.5
7 (EDTA Control)	6	6	0	12.5
8 (EDTA Low)	6	6	8	12.5
9 (EDTA High)	6	6	16	12.5

a Group 1 received empty gelatin capsules only.

Purpose of study

The purpose of this study was to evaluate GI toxicity and TK of risedronate (NE-58095) when dosed once weekly with two fixed doses of EDTA. The study was requested by the FDA to evaluate effects of EDTA on risedronate toxicity, particularly GI toxicity.

Risedronate was dosed at levels expected to be a NOAEL or induce very low gastric toxicity (8 mg/kg/dose) and a dose expected to be have low to moderate gastric toxicity (16 mg/kg/dose). EDTA was dosed at 2.5 mg/kg/dose or at 12.5 mg/kg/dose. On a mg/kg basis, this is the clinical dose of EDTA (b) (4) for a 40 kg woman and a 5x multiple. In absolute terms, this is approximately 20 and 100 mg for dogs weighing 8 kg on average. The risedronate doses (8, 16 mg/kg) are large multiples of the human dose of 35 mg (0.6 mg/kg), on a mg/kg or mg/m^2 basis. No effects from EDTA were expected as no significant toxicity was noted in a previous chronic dietary toxicity study in dogs at 250 mg/kg. However, the impact of food on EDTA toxicity is unknown.

Dosing procedure
Test article(s) were dispensed into gelatin capsules. Capsules were prepared by adding the EDTA amount to the capsule first and then the risedronate. The capsules were administered once each week for 14 weeks (14 doses). Doses were based on the most recently recorded body weights. Control animals received empty gelatin capsules. Immediately following the administration of the capsule, animals were administered a flush of approximately 10 mL of reverse osmosis water. Dosing occurred in the morning following an overnight fast. Food was returned to the animals after at least 2 hours postdose. The EDTA concentrations in this volume of 10 mL would be (20-100mg/10mL=2-10g/L=) **5.4-27mM** (Mw EDTA=372) and risedronate concentrations would be **18-36 mM**. Dilution by intestinal fluid with a Ca concentration of 1-2.5 mM would lower these concentrations.

Toxicokinetic Analyses
Blood samples were taken on Days 1, 22, 57, and 92, at 0.25, 0.5, 1, 2, 4, 6, 10, 24, and 48 hours postdose. All time points collected for Groups 2, 3, 5, 6, 8, and 9 were analyzed for the free base of NE-58095. Only the 1-hour time point from Groups 1, 4, and 7 was analyzed.

Clinical Pathology
Clinical pathology sampling was conducted at least twice during the predose phase (blood tests; once for urinalysis) and Day 22 (clinical chemistry only) and Days 59 and 94 (2 days following Doses 9 and 14, respectively) for hematology, coagulation, clinical chemistry, and urinalysis.

Terminal Procedures
On Day 94, all animals were fasted overnight and anesthetized with sodium pentobarbital, exsanguinated, and necropsied on Day 95 (3 days following last dose). A standard panel of tissues was collected. All tissues were embedded in paraffin, sectioned, stained with hematoxylin and eosin, and examined microscopically.

Observations and Results (see Table 1)

Mortality
- None

Clinical Signs

- Nonformed feces was seen in all animals but was not clearly treatment-related.
- One male (Grp 9) lost weight between D1-D18 and had abnormal feces in Wk3. Clinical pathology data showed abnormalities (Ca increase, AST increase, TBA increase) and animal was put on dosing holiday from D22-D36. Dosing was resumed on D36 and animal completed study.

Body Weights

- Decrease in males in all RIS-treated w/wo EDTA. Effect most pronounced in Grp9M.

Body weight and Body weight gain (kg)

	1	2	3	4	5	6	7	8	9
RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*8* *0*	*16* *0*	*0* *2.5*	*8* *2.5*	*16* *2.5*	*0* *12.5*	*8* *12.5*	*16* *12.5*
Males Day 1	8.2	8.2	8.4	8.3	8.2	8.1	8.0	7.9	8.2
Males Day 95	10.7	9.9	10.0	10.9	9.5*	9.9	10.3	10.0	9.1*
Males (D1-D95)	2.5	1.8*	1.6*	2.6	1.4*	1.8	2.3	2.2	0.9*
Females Day 1	6.0	6.1	6.2	6.1	6.1	6.1	6.1	6.1	6.1
Females Day 95	7.3	7.4	7.3	7.7	7.6	7.1	7.2	7.5	7.4
Females (D1-D95)	1.3	1.3	1.1	1.7	1.5	1.0	1.1	1.3	1.3

*significantly different from controls

Feed Consumption

- Food consumption was decreased at various times in the study in males at 8 or 16 mg/kg w/wo EDTA. Effect was not obvious in groups treated with 12.5 mg/kg EDTA.
- This led to a marked decrease in BW and BW gain in the males in the 16/12.5 mg/kg group (Grp 9M). The BW effect was considered adverse in this group.

Ophthalmoscopy

- Not evaluated

ECG

- Not evaluated

Hematology

- RBC parameters: minimal decrease in 16 mg/kg M,F w/wo 12.5 mg/kg EDTA and in 8 mg/kg F w 12.5 mg/kg EDTA (Grps 3M,3F; Grp 8F; Grps 9M,9F) (Days 59, 94). Affected groups had highest RIS exposure. Effect appeared to be enhanced by EDTA.
- Neutrophil count (abs, rel): minimal increase at 8 and 16 mg/kg w/wo EDTA (Grps 3,5, 6,8,9), in M and F (Days 59, 94). Effect not obviously altered by EDTA.

Clinical Chemistry

- No changes in glucose, BUN, creatinine
- Minimal increase in TP and GLOB in M/F at 16 mg/kg (w/wo edta)
- Minimal decrease in ALB and ALB/GLOB in M/F at 16 mg/kg (w/wo edta)

AST (U/L) (dose-dependent increase due to RIS treatment)

- Effect exacerbated by 12.5 mg/kg EDTA at 8 mg/kg probably secondary to increased RIS exposure

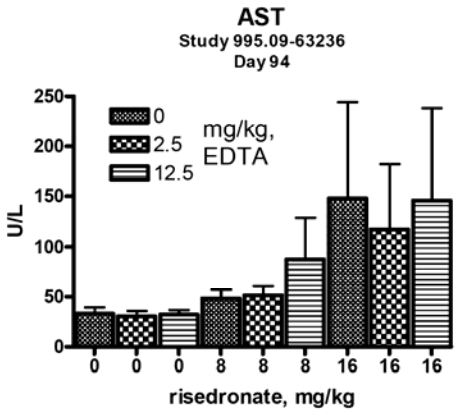
	1	2	3	4	5	6	7	8	9
RIS (mg/kg)	*0*	*8*	*16*	*0*	*8*	*16*	*0*	*8*	*16*
EDTA (mg/kg)	*0*	*0*	*0*	*2.5*	*2.5*	*2.5*	*12.5*	*12.5*	*12.5*
Males Day 94	34	46*	200*	33	54*	113*	35	**104***	182*
Females Day 94	32	50*	96*	28	49*	123*	30*	**72***	110*

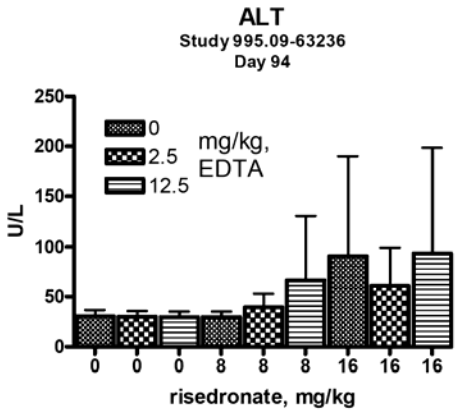
*significantly different from (respective) control group(s)

ALT (U/L) (dose-dependent increase due to RIS treatment)

- Effect exacerbated by 12.5 mg/kg EDTA at 8 mg/kg probably secondary to increased RIS exposure

	1	2	3	4	5	6	7	8	9
RIS (mg/kg)	*0*	*8*	*16*	*0*	*8*	*16*	*0*	*8*	*16*
EDTA (mg/kg)	*0*	*0*	*0*	*2.5*	*2.5*	*2.5*	*12.5*	*12.5*	*12.5*
Males Day 94	34	32	137*	33	41	55*	29	**53***	107*
Females Day 94	28	28	44*	27	38	67*	31	**44***	81*





Ca (mg/dL) (dose-dependent decrease due to RIS treatment)

- Effect not altered by EDTA even though this increased RIS absorption/exposure

	1	2	3	4	5	6	7	8	9
RIS (mg/kg)	*0*	*8*	*16*	*0*	*8*	*16*	*0*	*8*	*16*
EDTA (mg/kg)	*0*	*0*	*0*	*2.5*	*2.5*	*2.5*	*12.5*	*12.5*	*12.5*
Males Day 94	11.8	10.7*	11.0*	11.4*	10.8*	10.8*	11.7	11.1*	10.8*
Females Day 94	11.5	10.9*	10.6*	11.5	11.0	10.7*	11.4	10.7*	10.8*

Phos (mg/dL) (dose-dependent decrease due to RIS treatment)

- Effect not altered by EDTA even though this increased RIS absorption/exposure

	1	2	3	4	5	6	7	8	9
RIS (mg/kg)	*0*	*8*	*16*	*0*	*8*	*16*	*0*	*8*	*16*

EDTA (mg/kg)	*0*	*0*	*0*	*2.5*	*2.5*	*2.5*	*12.5*	*12.5*	*12.5*
Males Day 94	5.4	3.5*	2.9*	5.6	3.5*	3.2*	4.9	3.8*	2.7*
Females Day 94	5.5	3.6*	3.9*	5.5	3.4*	3.5*	4.9	3.4*	3.3*

TBA (total bile acid) (umol/L) (increase in some animals due to RIS treatment)

- Effect not altered by EDTA

	1	2	3	4	5	6	7	8	9
RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*8* *0*	*16* *0*	*0* *2.5*	*8* *2.5*	*16* *2.5*	*0* *12.5*	*8* *12.5*	*16* *12.5*
Males Day 94	4	4	78#	3	4	12#	4	4	48#
Females Day 94	3	2	44#	2	3	64#	5	5	59#

#change not significant due to large variation

Urine Chemistry and Urinalysis

- No changes

Gross Pathology

- Large and discolored (dark red), multiple or bilateral abdominal veins in the adipose tissue near the kidney (listed as *vein, other*) in Grps 3, 6, 9 (16 mg/kg), correlated microscopically with prominent and often multiple blood-filled veins. Effect was not altered by EDTA.
- Discolored mesenteric lymph nodes in Grp 9F (16 mg/kg+12.5 EDTA), correlated microscopically to sinus erythrocytes.

Text Table 2
Incidence of Selected Macroscopic Findings - Males and Females

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	12	12	12	12	12	12	12	12	12
Vein (Other)									
Large	0	0	5	0	0	2	0	0	5
Discolored	0	0	2	0	0	1	0	0	0
Mesenteric Lymph Node									
Discolored	0	0	0	0	0	0	0	0	2

Organ Weights

- Kidney: Increase in weight (abs, rel), related to microscopic findings of de/regeneration, inflammation, enlarged epithelium.
- Effect not altered by EDTA

Text Table 1
Test Article-Related Kidney Weight Changes - Percent Difference from Controls

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
Males									
Mean Absolute Weight	0	↓2.2	↑18	↑4.2	↑1.9	↑14.8	↓3.9	↑5.7	↑22.9
Mean Kidney-to-Brain Weight %	0	↓2.8	↑23.1[a]	↓0.4	↑1.6	↑17.3	↓2.6	↑5.7	↑24.7[a]
Mean Kidney-to-Body Weight %	0	↑6.6	↑27.2[a]	↑2.3	↑16.1	↑22.7[a]	↓0.9	↑12	↑45.4[a]
Females									
Mean Absolute Weight	0	↑23.9	↑41.3[a]	↑16.2	↑20.3[a]	↑40.07[a]	↑6.6	↑24.6[a]	↑38.9[a]
Mean Kidney-to-Brain Weight %	0	↑19.7[a]	↑28[a]	↑6.1	↑8	↑31.6[a]	↓3.4	↑16[a]	↑27[a]
Mean Kidney-to-Body Weight %	0	↑20[a]	↑41.5[a]	↑7.5	↑15.8	↑47[a]	↑6.1	↑18.9[a]	↑34.9[a]

a Statistically significant.

Histopathology
Tables show incidences and grade: a= minimal, b = slight, c = moderate) (N=6/s/g)

Liver:

- Hepatocellular atrophy, vacuolation, glycogen decrease, increased with RIS-dose/treatment:
- Incidence higher in males than females.
- Findings weakly correlated with increased serum AST, ALT, TBA.
- Atrophy was enhanced in some EDTA groups, appeared correlated to AUC (D92) of RIS in M and F. No effect of EDTA only.
- NOAEL<8 mg/kg

		Group	1	2	3	4	5	6	7	8	9
		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*
Liver	M	Atrophy, hepatocellular						**1 a**	3 ab	1 a	**5 ab**
	M	Vacuolation, hepatocyte							2 ab		1 b
	M	Glycogen decrease	1	2	1	1	1		3	1	6
	F	Atrophy, hepatocellular				1 a		**2 a**	2 a	2 a	**4 a**

N=6/s/g; grade: a= minimal, b = slight, c = moderate

Kidney:

- Degeneration, regeneration, inflammation and enlarged epithelial cells, all related to RIS-dose/treatment
- Findings slightly more frequent in males than females
- Findings increased with 12.5 mg/kg EDTA, at both risedronate doses. Increase probably correlated to systemic RIS- AUC.

		Group	1	2	3	4	5	6	7	8	9
		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*

Kidney	M	Degeneration, tubule epith				1 a		**3 a**	6 ab	1 a	3 ab
		Regeneration, tubule epith	4 a	3 a	2 a	3 a	4 a	4 a	5 ab	6 ab	**6 abc**
		Inflammation, chronic, interstitial		1			1 a	1 a	3 a	4 a	4 a
		Enlargement, tub epith cell, medulla				1 a		**4 a**	6 ab	3 ab	6 ab
	F	Degeneration, tubule epith					2 a	**4 a**	3 a	1 b	**4 ab**
		Regeneration, tubule epith	1 a	1 a	1 a	3 a	2 ab	**5 ba**	4 ab	2 bc	**6 abc**
		Inflammation, chronic, interstitial		3 a		3 a	1 a	**4 a**	3 a	4 ab	**5 ab**
		Enlargement, tub epith cell, medulla				2 a	1 a	**5 a**	3 a	3 ab	**5 ab**

N=6/s/g; grade: a= minimal, b = slight, c = moderate

Stomach:

- Mineralization, single cell necrosis, inflammation, hyperplasia, all related to RIS-dose/treatment
- Necrosis, inflammation and regenerative hyperplasia were increased in females treated with 8 mg/kg RIS by 12.5 mg/kg but not 2.5 mg/kg EDTA, suggesting potential exacerbation of local RIS toxicity by EDTA - or increase in systemically induced stomach toxicity due to RIS exposure increase. This was not seen in 8 mg/kg males. Absence of exacerbation at 16 mg/kg RIS may be due to plateau effect.
- Sponsor concluded that, based on the fact that exacerbation was seen only in females at 8 mg/kg, "*overall there was no apparent effect of EDTA on the stomach effects seen with risedronate*".

		Group	1	2	3	4	5	6	7	8	9
		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*
Stomach	M	Mineralization, epithelium	2 a		1 a	1 a	1 a	2 ab	3 ab	4 ac	4 abc
		Single cell necrosis, mucosa				6 ab	4 ab	4 ab	6 abc	5 abc	4 abc
		Inflammation, chronic, mucosa		1 b		4 a	1 b	1 a	6 ab	1 b	3 ab
		Regenerative hyperplasia, pits				2 ab	3 ab	2 a	3 ab	3 a	4 ab
	F	Mineralization, epithelium		1 a					3 abc	2 ab	1 a
		Single cell necrosis, mucosa				1 a	1 a	**5 ab**	4 ab	3 a	4 ab
		Inflammation, chronic, mucosa				1 a	1 a	**3 a**	3 ab	2 a	2 a
		Regenerative hyperplasia, pits						**4 a**	3 a	4 a	3 a

N=6/s/g; grade: a= minimal, b = slight, c = moderate

Mesenteric lymph node:

- Sinus erythrocytes
- In 8 mg/kg dose groups, EDTA 12.5 mg/kg increased the finding probably due to increased RIS exposure

		Group	1	2	3	4	5	6	7	8	9

		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*
Lymph node	M	Sinus erythrocytes	2 a	2 a	3 a	1 a	1 a	**3 ab**	5 abc	5ab	5 bc
	F	Sinus erythrocytes		1 a			1 a	**4 ab**	5 ab	3 ab	3 bc

N=6/s/g; grade: a= minimal, b = slight, c = moderate

Vein (abdominal):

- Increased prominence of abdominal vein (in adipose tissue near kidney) at 16 mg/kg. Vessels were sometimes thickened and had plump intimal/medial cells.
- EDTA did not affect this finding.

		Group	1	2	3	4	5	6	7	8	9	
		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*	
Vein, abdominal	M	Increased prominence							1c	0	1 a	
	F	Increased prominence							3bc	1a	1 a	

N=6/s/g; grade: a= minimal, b = slight, c = moderate

Testes:

- Hypospermatogenesis increased at 16 mg/kg (average of all groups)
- Multinucleated cells appeared increased in RIS + 12.5 mg/kg EDTA groups

		Group	1	2	3	4	5	6	7	8	9
		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*
Testis	M	Hypospermatogenesis	4 ac	3 ab	1 a	0	5 ab	1 c	4 ab	4 ac	4 b
		Multinucleated giant cells	2 a	3 a	1 a	1 a		**3 ab**	2 a	1 a	**5** abc

N=6/s/g; grade: a= minimal, b = slight, c = moderate

Heart:

- Mineralization in the ascending aorta (mineralized deposits in tunica media) was observed in untreated control and 12.5 mg/kg EDTA groups.
- Incidence was increased by RIS at 16 mg/kg. Finding was also increased at 8 mg/kg + 12.5 mg/kg EDTA.

		Group	1	2	3	4	5	6	7	8	9
		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*
Heart/ ascending aorta	M	Mineralization	1 a				2 a	**2 b**	3b	1b	2ab
	F	Mineralization			1 a			**3ab**	2b	2b	1a

N=6/s/g; grade: a= minimal, b = slight, c = moderate

Bone:

- Increase in bone in rib, sternum and nasal turbinates in males and females was RIS-dose-related. This is pharmacologic effect of drug.
- Severity/incidence minimally increased in some 12.5 mg/kg EDTA groups.

		Group	1	2	3	4	5	6	7	8	9
		RIS (mg/kg) *EDTA (mg/kg)*	*0* *0*	*0* *2.5*	*0* *12.5*	*8* *0*	*8* *2.5*	*8* *12.5*	*16* *0*	*16* *2.5*	*16* *12.5*
Bone	M	Rib, PS persistence/hypertrophy				6 ab	6 ab	**6 ba**	6 ab	6 ab	**6 ba**
		Sternum, PS persistence/hypertrophy				6 b	6 b	6 b	6 b	6 b	6 b
		Nasal turbinates, increased bone				4 a	3 ab	**5 ab**	6 ab	5 ab	**6 ba**
	F	Rib, PS persistence/hypertrophy				6 ab	6 ab	6 ab	6 ab	6 ba	**6 ba**
		Sternum, PS persistence/hypertrophy				6 b	6 b	6 b	6 b	5 b	6 b
		Nasal turbinates, increased bone				4 a	4 a	3 ab	3 ab	6 ab	5 ab

PS primary spongiosa
N=6/s/g; grade: a= minimal, b = slight, c = moderate

Toxicokinetics

Findings:

- Risedronate was rapidly absorbed, with Tmax = 0.5-1.5h (range D1-D92)
- T1/2 = 6.8-14.8h (range, D1-D92)
- More than dose-proportional increase in exposure (Cmax and AUC) with 8 and 16 mg/kg RIS
- Dose-related increase in Cmax and AUC with 2.5 and 12.5 mg/kg EDTA for the 8mg/kg RIS groups, and increase in Cmax and AUC with 12.5 mg/kg EDTA (not 2.5 mg/kg) for the 16 mg/kg RIS groups.
- Most pronounced increase in RIS exposure was seen in 8 mg/kg groups dosed with 12.5 mg/kg EDTA (3x-9x).
- Exposure in 8 RIS+12.5 EDTA groups was similar to exposure in 16 RIS groups
- Increased exposure with multiple dosing, indicating drug accumulation (AR>1), exacerbated by EDTA
- Exposure (Cmax, AUC) appeared to be higher in males than in females

Risedronate exposure (AUC, ngxh/mL) (Day 63+92 average)

		AUC (ris) (ngxh/mL)		
RIS	EDTA	M	F	Avg (M+F)
8	0	1309	1169	1,239
	2.5	2754	2683	2,719
	12.5	9383	6697	8,040
16	0	21588	7607	(14,598)
	2.5	11129	10587	10,858
	12.5	32529	19813	26,171

Table 4.1
Summary of mean toxicokinetic parameters of NE-58095 in dog serum

NE-58095 Dose Level (mg/kg/dose)	EDTA Dose Level (mg/kg/dose)	Sex	Parameter	Day 1	Day 22	Day 63	Day 92
8	0	M	C_{max}	457	528	529	590
8	2.5	M	C_{max}	518	830	919	507
8	12.5	M	C_{max}	1463	1221	2703	1415
8	0	M	AUC_{0-t}	1008	1268	1178	1440
8	2.5	M	AUC_{0-t}	1865	2598	3380	2128
8	12.5	M	AUC_{0-t}	4623	4909	10784	7982
8	0	M	AR AUC_{0-t}	NA	1.09	1.07	1.52
8	2.5	M	AR AUC_{0-t}	NA	1.75	1.90	1.83
8	12.5	M	AR AUC_{0-t}	NA	1.10	2.48	2.15
8	0	F	C_{max}	382	575	517	423
8	2.5	F	C_{max}	385	649	663	1264
8	12.5	F	C_{max}	947	1018	1753	1685
8	0	F	AUC_{0-t}	705	1373	1260	1078
8	2.5	F	AUC_{0-t}	880	1816	1960	3406
8	12.5	F	AUC_{0-t}	2556	3294	6510	6883
8	0	F	AR AUC_{0-t}	NA	2.03	1.93	1.77
8	2.5	F	AR AUC_{0-t}	NA	2.10	2.42	4.06
8	12.5	F	AR AUC_{0-t}	NA	1.56	2.91	3.47
16	0	M	C_{max}	1381	3355	3022	2860
16	2.5	M	C_{max}	1277	1768	2138	1797
16	12.5	M	C_{max}	3525	3362	4303	3902
16	0	M	AUC_{0-t}	5314	16146	20870	22306
16	2.5	M	AUC_{0-t}	5601	6857	10867	11390
16	12.5	M	AUC_{0-t}	15439	16561	27244	37814
16	0	M	AR AUC_{0-t}	NA	4.88	6.36	7.03
16	2.5	M	AR AUC_{0-t}	NA	1.97	2.49	2.66
16	12.5	M	AR AUC_{0-t}	NA	1.00	1.92	2.61
16	0	F	C_{max}	1030	1917	2042	1671
16	2.5	F	C_{max}	1245	1612	2255	1677
16	12.5	F	C_{max}	2148	2700	3130	2462
16	0	F	AUC_{0-t}	3764	9293	8703	6511
16	2.5	F	AUC_{0-t}	5231	7678	11462	9712
16	12.5	F	AUC_{0-t}	9848	12599	21592	18033
16	0	F	AR AUC_{0-t}	NA	2.48	2.31	1.75
16	2.5	F	AR AUC_{0-t}	NA	1.67	2.41	2.51
16	12.5	F	AR AUC_{0-t}	NA	1.61	2.78	2.23

Table 1. Summary of the Mean Toxicokinetic Parameters for NE-58095 in Dog Serum: Day 1

Dose Group	NE-58095 Dose Level (mg/kg/dose)	EDTA Dose Level (mg/kg/dose)	Sex		C_{max} (ng/mL)	DN C_{max} (ng/mL)/ (mg/kg/dose)	T_{max} (hr)	T_{last} (hr)	AUC_{0-t} (ng*hr/mL)	DN AUC_{0-t} (ng*hr/mL)/ (mg/kg/dose)	$t_{1/2}$ (hr)
2	8	0	M	Mean	457	57.1	0.458	41.7	1008	126	7.72
				SD	254	31.8	0.292	15.5	644	80	2.24
				N	6	6	6	6	6	6	6
			F	Mean	382	47.8	1.08	48.0	705	88.2	9.87
				SD	188	23.5	0.49	0	296	36.9	1.42
				N	6	6	6	6	6	6	6
3	16	0	M	Mean	1381	86.3	1.25	48.0	5314	332	7.75
				SD	844	52.7	0.61	0	4088	255	0.79
				N	6	6	6	6	6	6	6
			F	Mean	1030	64.3	1.50	48.0	3764	235	7.60
				SD	127	7.9	0.55	0	450	28	0.51
				N	6	6	6	6	6	6	6
5	8	2.5	M	Mean	518	64.8	1.33	48.0	1865	233	8.76
				SD	335	41.8	0.52	0	1124	141	1.28
				N	6	6	6	6	6	6	6
			F	Mean	385	48.1	0.833	48.0	880	110	10.2
				SD	140	17.5	0.258	0	367	46	1.3
				N	6	6	6	6	6	6	6
6	16	2.5	M	Mean	1277	79.8	1.17	48.0	5601	350	7.75
				SD	644	40.2	0.68	0	3826	239	1.25
				N	6	6	6	6	6	6	6
			F	Mean	1245	77.8	1.50	48.0	5231	327	7.19
				SD	516	32.3	0.55	0	2057	129	0.44
				N	6	6	6	6	6	6	6
8	8	12.5	M	Mean	1463	183	0.708	48.0	4623	578	7.33
				SD	615	77	0.332	0	1869	234	0.15
				N	6	6	6	6	6	6	6
			F	Mean	947	118	0.833	48.0	2556	319	8.30
				SD	402	50	0.258	0	1409	176	0.99
				N	6	6	6	6	6	6	6
9	16	12.5	M	Mean	3525	220	0.833	48.0	15439	965	6.75
				SD	1143	71	0.258	0	5455	341	0.51
				N	6	6	6	6	6	6	6
			F	Mean	2148	134	1.08	48.0	9848	616	7.01
				SD	1261	79	0.49	0	6186	387	0.60
				N	6	6	6	6	6	6	6

Table 4. Summary of the Mean Toxicokinetic Parameters for NE-58095 in Dog Serum: Day 92

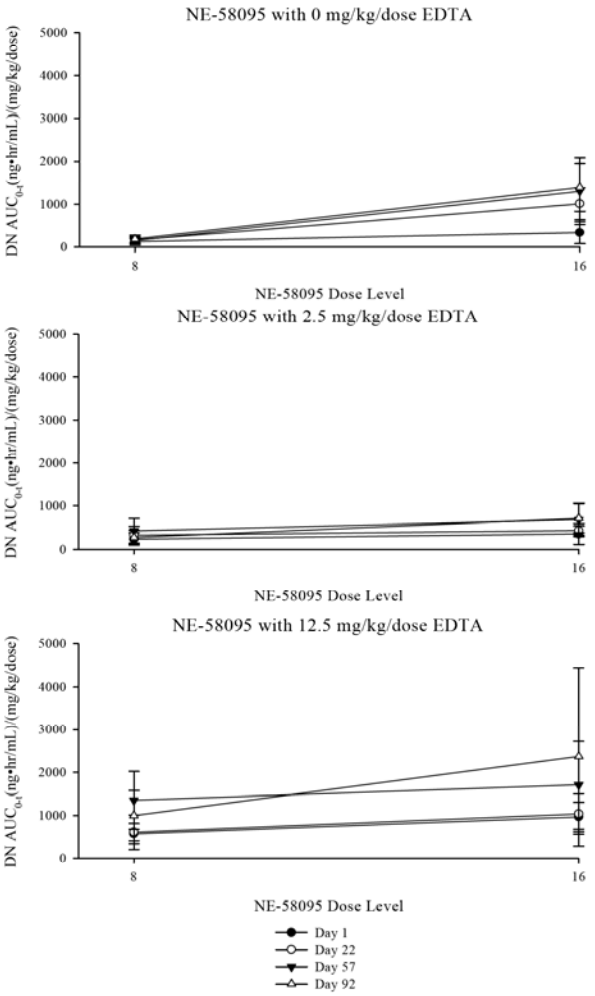
Dose Group	NE-58095 Dose Level (mg/kg/dose)	EDTA Dose Level (mg/kg/dose)	Sex		C_{max} (ng/mL)	DN C_{max} (ng/mL)/ (mg/kg/dose)	T_{max} (hr)	T_{last} (hr)	AUC_{0-t} (ng*hr/mL)	DN AUC_{0-t} (ng*hr/mL)/ (mg/kg/dose)	$t_{1/2}$ (hr)	AUC_{0-t} R
2	8	0	M	Mean	590	73.7	0.875	48.0	1440	180	12.0	1.52
				SD	311	38.9	0.628	0	762	95	1.95	0.51
				N	6	6	6	6	6	6	5	5
			F	Mean	423	52.9	1.17	48.0	1078	135	14.6	1.77
				SD	185	23.1	0.41	0	417	52	3.88	1.00
				N	6	6	6	6	6	6	6	6
3	16	0	M	Mean	2860	179	1.00	48.0	22306	1394	14.8	7.03
				SD	981	61	0.55	0	8943	559	5.3	6.07
				N	6	6	6	6	6	6	6	6
			F	Mean	1671	104	1.25	48.0	6511	407	10.8	1.75
				SD	551	34	0.61	0	2105	132	1.5	0.54
				N	6	6	6	6	6	6	6	6
5	8	2.5	M	Mean	507	63.4	1.00	48.0	2128	266	12.6	1.83
				SD	213	26.7	0	0	1380	173	2.4	2.12
				N	6	6	6	6	6	6	6	6
			F	Mean	1264	158	0.833	48.0	3406	426	11.0	4.06
				SD	575	72	0.258	0	1560	195	1.3	1.96
				N	6	6	6	6	6	6	6	6
6	16	2.5	M	Mean	1797	112	0.917	48.0	11390	712	12.9	2.66
				SD	532	33	0.585	0.0	5387	337	4.4	1.48
				N	6	6	6	6	6	6	5	6
			F	Mean	1677	105	1.42	48.0	9712	607	13.0	2.51
				SD	599	37	0.66	0	6196	387	5.8	2.66
				N	6	6	6	6	6	6	5	6
8	8	12.5	M	Mean	1415	177	0.750	48.0	7982	998	12.4	2.15
				SD	656	82	0.274	0	4639	580	4.5	2.24
				N	6	6	6	6	6	6	6	6
			F	Mean	1685	211	0.833	48.0	6883	860	12.0	3.47
				SD	753	94	0.258	0	4041	505	3.4	3.43
				N	6	6	6	6	6	6	6	6
9	16	12.5	M	Mean	3902	244	1.08	48.0	37814	2363	9.74	2.61
				SD	983	61	0.49	0	33222	2076	2.18	2.30
				N	6	6	6	6	6	6	5	6
			F	Mean	2462	154	1.33	48.0	18033	1127	13.7	2.23
				SD	1399	87	0.52	0	11743	734	7.26	1.32
				N	6	6	6	6	6	6	6	6

APPEARS THIS WAY ON ORIGINAL

2.6.7.3 Toxicokinetics: Overview of Toxicokinetic Data

Test Article: N

NE-58095 dose normalized AUC_{0-t} relationships in male dog serum



NE-58095 dose normalized AUC_{0-t} relationships in f

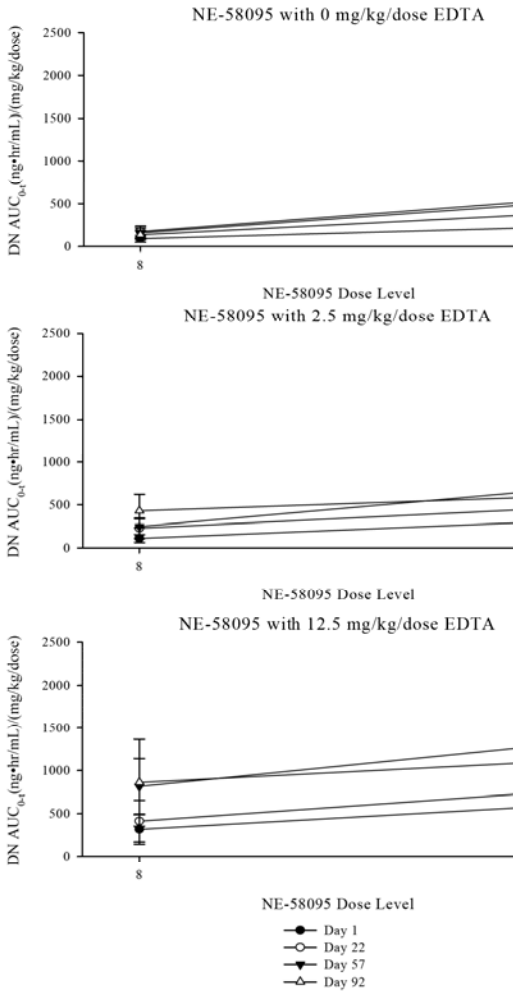
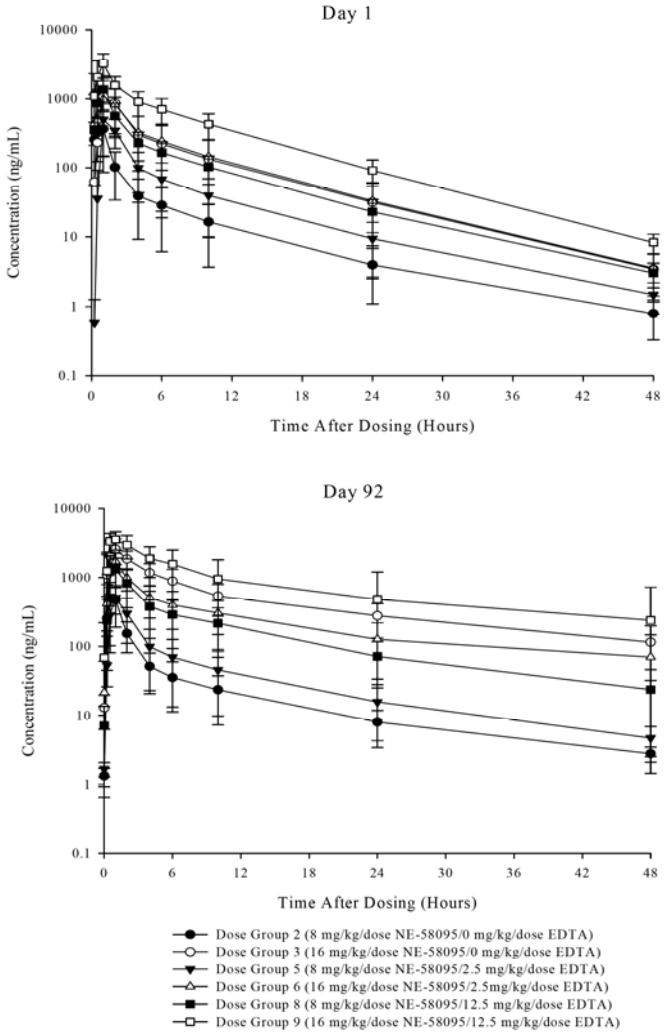


Figure 1.1
Mean concentrations (ng/mL) of NE-58095 in male dog serum as a function of dose



Note: Error bars represent standard deviations.

Stability and Homogeneity

Submitted data on test article (risedronate, EDTA) characterization, risedronate stability and test article formulation (risedronate + EDTA) stability were adequate.

Summary and Evaluation

Table 1 Findings 13-week dog study (risedronate and EDTA)

Risedronate dose	Finding	Incidence/severity exacerbated by EDTA (12.5 mg/kg)	NOAEL risedronate (mg/kg)	Exposure Multiple (based on AUC*)
8, 16 mg/kg	Reduced BW and BW gain; reduced FC (males only)	Yes (16 mg/kg)	< 8 mg/kg	<36x
	AST, ALT increase (M,F)	Yes (8 mg/kg)		
	Ca decrease (M,F)	No		
	P decrease (M,F)	Yes (16 mg/kg)		
	Bone, spongiosa persistence/hypertrophy	Yes (8, 16 mg/kg)		
	Liver: hepatocellular atrophy	Yes (8, 16 mg/kg)		
	Kidney: weight increase, de/regeneration, inflammation, enlarged epithelial cells	Yes (8, F 16 mg/kg)		
	Stomach: mineralization, single cell necrosis, inflammation, hyperplasia	Yes (8 mg/kg, F only)		
	Lymph node: sinus erythrocytes	Yes (8 mg/kg)		
	(Heart/ascending aorta: mineralization)	Yes (8 mg/kg)		
16 mg/kg	RBC decrease, neutrophil increase (M,F)	No	8 mg/kg	36x
	Albumin decrease, Globulin increase	No		
	Bile acid increase	No		
	Liver: hepatocyte vacuolation, glycogen decrease	No		
	Stomach: epithelial mineralization increase	No		
	Vein: enlargement, discoloration, prominence	No		
	Testis: hypospermatogenesis, multinucleated giant cells	No,Yes		
	Heart/ascending aorta: mineralization	No		

*$AUC_{0\text{-}last}$ in human: 34 ng.hr/ml, Cmax =14.1 ng/mL (Study #2008119, 2-period cross-over BE study with Phase 3 and commercial 35 mg DR formulations)

Table 2 Toxicokinetics 13-week dog study (risedronate)

Risedronate exposure (AUC, ngxh/mL) (Day 63+92 average)

		AUC (Risedronate) (ngxh/mL)		
Risedronate (mg/kg)	EDTA (mg/kg)	Males	Females	Average (Males/Females)
8	0	1309	1169	1,239
	2.5	2754	2683	2,719
	12.5	9383	6697	8,040
16	0	21588	7607	(14,598)
	2.5	11129	10587	10,858
	12.5	32529	19813	26,171

Table 3 Dose and AUC multiples 13-week dog study (risedronate and EDTA)

		Dog	Human*	Dog: Human multiple
Risedronate	Dose (mg/kg)	8	0.54	15x
		16	0.54	30x
	AUC (ngxh/mL)**	1,239	34	36x
		7,607 (Females)	34	224x
EDTA	Dose (mg/kg)	2.5	1.5	1.7x
		12.5	1.5	8.3x
	Dose (mg/m2)	2.5 x 18 = 45	1.5 x 37 = 55.5	0.8x
		12.5 x 18 = 225	1.5 x 37 = 55.5	4x
	Dose (mg)	20	100	0.2x
		100	100	1x

* 35 mg risedronate with (b) (4) EDTA delayed release tablet
** Dog AUC of risedronate in presence of 2.5 mg/kg EDTA

Summary of dog study findings

A 13-week toxicity study was conducted in beagle dogs with weekly oral doses of risedronate (8 or 16 mg/kg) with or without EDTA (2.5, 12.5 mg/kg).
The main effects of risedronate at both 8 and 16 mg/kg included the pharmacologic effect on bone (persistence/hypertrophy of primary spongiosa in rib, sternum and nasal turbinates), decrease in food consumption and body weight/gain in males, serum Ca and P decreases, ALT and AST increases, kidney weight increase and histopathological changes in kidney (tubular epithelial de/regeneration, medullary tubule epithelial cell enlargement, chronic interstitial inflammation), liver (centrilobular hepatocellular atrophy) and stomach (single cell necrosis, gastric pit regenerative hyperplasia, chronic inflammation). At 16 mg/kg there were also hematology changes (RBC decrease, neutrophil increase) increases in bile acid, increase in globulin and decrease in albumin, liver hepatocellular vacuolation and glycogen decrease, stomach epithelial mineralization, lymph node sinus erythrocytes, vein enlargement and prominence, testis hypospermatogenesis and multinucleated giant cells and aorta mineralization. A few of the latter findings (RBC decrease, lymph node erythrocytes, aorta mineralization) also occurred at 8 mg/kg + 12.5 mg/kg EDTA.

EDTA alone had no adverse effects and the addition of EDTA to risedronate did not cause any new toxicities beyond those already observed in the risedronate-only groups. However, EDTA (12.5 mg/kg) exacerbated several risedronate-induced systemic toxicities (AST and ALT increases, kidney weight increase, histologic changes in kidney, liver, lymph nodes, testis, heart/aorta) and the pharmacologic effect on bone. EDTA (12.5 mg/kg) also enhanced stomach irritation in females but not males treated with 8 mg/kg.

Risedronate exposure (Cmax, AUC) was increased >>2x with the increase of dose from 8 to 16 mg/kg. Exposure also increased over the first 8 weeks of the study indicating drug accumulation. Non-linearity in the dose-exposure relationship for bisphosphonates

has been observed previously and may be due to risedronate enhancing its own absorption due to tight junctional Ca chelation and altered paracellular transport (Lin et al, 1994). Exposure to risedronate was also markedly increased by EDTA with the most pronounced effect in the 8 mg/kg groups. Exposure multiples for risedronate (in the absence of EDTA in the dogs), based on comparison to human AUC with the 35 mg DR tablet (AUC = 34 ngxh/mL), were 36x (at 8 mg/kg) and 224x (at 16 mg/kg in females).

The NOAEL for risedronate-related toxicities was ≤ 8 mg/kg, i.e., **≤36x** the human AUC for risedronate with the 35 mg DR tablet. The NOAEL for systemic toxicity enhancement by EDTA was 2.5 mg/kg, or **0.8x** human dose of EDTA (mg/m^2 basis). The NOAEL for the exacerbation of stomach toxicity (in females) by EDTA was also 2.5 mg/kg, or **0.8x** the human (b) (4) dose (mg/m^2 basis). However, the difference in dosing procedure between dogs and humans (fasted vs non-fasted, capsule vs DR tablet) may limit the accuracy of the EDTA dose comparisons.

Evaluation of dog study findings

Risedronate

The liver, kidney and stomach toxicities and the bone effects of risedronate were expected and have previously been observed (APPENDIX II). In chronic dog toxicity studies of up to 1 year with daily dosing, risedronate caused toxicities in GI tract (stomach, esophagus, intestine), kidney, liver, lung (vessels), lymph nodes, testis and pancreas. NOAEL was 4 mg/kg. In 6- and 12-month monthly dosing studies, effects included toxicity in stomach, esophagus, kidney and liver. NOAEL was <16 mg/kg for local (stomach, esophagus) toxicity and 16 mg/kg for systemic (kidney, liver) toxicities. Aorta mineralization has not previously been observed and the significance of this finding is unclear. The electrolytre changes (Ca, P decrease) are expected effects of high doses of bisphosphonates. Hypocalcemia is due to Ca-chelation and hypophosphatemia is probably the result of the ensuing PTH increase. The pharmacodynamic effect on bone was observed in all studies conducted in younger dogs in which the epiphyses were not yet closed and primary spongiosa was present in bone tissue examined, including the current 13-week study.

The intestinal toxicity observed in the daily or monthly dosing studies was not observed in the current 13-week study. Esophageal toxicity was observed in the daily study and the 6-month study in older (16-17-month) dogs, but was not seen in the 13-week study or the 12-month study, both conducted in younger (5-7-month) dogs. The duration and doses in the 13-week study were probably insufficient to produce more extensive GI toxicity. The margin of safety (i.e. AUC multiple at NOAEL) for local toxicity was similar in the 13-week study to that obtained in the monthly studies, while the safety margin for systemic toxicity was lower in the 13-week study. Safety margins obtained in weekly or monthly dosing studies were both smaller than those obtained in daily dosing studies. Large exposure multiples between the NOAEL in animals and the clinical dose support the use of the proposed 35 mg weekly DR risedronate product.

Dose frequency	Duration; Doses	NOAEL	AUC multiple at NOAEL	
			Local (stomach,	Systemic (kidney,

			esophagus, intestine) toxicity	liver) toxicity
Daily	12-mo study 0, 4, 8, 16, 32 mg/kg	4	95x	95x
Weekly	13-wk study 0, 8, 16 mg/kg (this submission)	<8	<36x (stomach only)	<36x
Monthly	6-mo study; 12-mo study 0, 16, 32, 64 mg/kg	<16 (local), 16 (systemic)	<37x	37x

AUC multiples based on total drug

Risedronate +/- EDTA

The dog study was designed to produce no or minimal gastric toxicity at the low 8 mg/kg dose and low to moderate gastric toxicity at the high 16 mg/kg dose and evaluate the effect of EDTA particularly on GI toxicity. The main effect of EDTA was to increase risedronate exposure and increase all toxicities, including systemic and gastric toxicity. EDTA alone did not have any effects. The increase in systemic toxicity was probably due to the EDTA-induced increase in systemic exposure (Cmax and/or AUC). This was supported by the fact that in females, toxicity as well as exposure in the 8 mg/kg +12.5 mg/kg EDTA group was similar to that observed in the 16 mg/kg group without EDTA.

Risedronate caused the expected stomach toxicity, which is believed to be a local effect although the occurrence of GI toxicity in studies with IV bisphosphonates has suggested a systemic component. The exacerbation of stomach toxicity by EDTA at the low risedronate dose is most likely a direct (local) effect of EDTA on the gastric epithelium. It is unclear why it was only observed in the female dogs. Possibly the lack of an effect was due to an already high incidence of gastric lesions in absence of EDTA in males. Sponsor concluded that, based on the fact that exacerbation was seen only in females at 8 mg/kg, "*overall there was no apparent effect of EDTA on the stomach effects seen with risedronate*". Reviewer concludes that the EDTA effect in females was significant and the data suggest that GI toxicity may be enhanced with the DR tablet.
The clinical relevance of the stomach findings may be limited due to differences between dog and humans in (1) risedronate doses and (2) drug formulations. The lack of lower intestinal toxicity in the EDTA groups may also have limited relevance due to differences in animal and human drug formulations and the short study duration.

Risedronate exposure

The effect of EDTA on risedronate exposure was a significant result of this study. The EDTA effect occurred at both EDTA doses (0.8x - 4x the human (b) (4) dose, based on mg/m^2) and was most pronounced at the 8 mg/kg risedronate dose. The cause of this exposure increase is likely to be an increase in absorption. Bisphosphonate (BP) absorption is believed to occur mainly in the upper part of the small intestine. EDTA (5.4-27 mM in 10 ml dosing fluid) may have complexed Ca in the intestinal fluid (1-2.5 mM Ca) preventing Ca-risedronate complexation and making more risedronate available for absorption. It is also possible that EDTA directly increased paracellular permeability as a result of tight junctional Ca and/or Mg chelation. EDTA has been found to increase absorption of bisphosphonates in rats (Janner et al, 1991; Lin et al,

1994). The authors also suggested this was either an indirect effect of Ca-complexation and prevention of insoluble Ca-BP complexes, or a direct effect of increasing paracellular permeability to the large anionic BP molecules. The shift in the dose response curve for EDTA's absorption enhancing effect in the current dog study, reflected by a larger AUC increase at 8 than at 16 mg/kg risedronate, may have been due to competition between risedronate and EDTA for Ca or other divalent cations in the intestine. It is unlikely that EDTA caused the exposure increase due to a decrease in renal excretion.

An increase in intestinal paracellular permeability by EDTA may enhance the absorption of risedronate as well as other co-administered polar drugs. This issue was discussed at the EOP2 meeting (See EOP2 meeting minutes) and in the NDA submission (Section 2.7.2.1. Clinical Pharmacology Summary). Sponsor believes that in vivo intestinal concentrations of EDTA will be <2 mM with the DR tablet and are not likely to influence the paracellular absorption of co-administered drugs. This conclusion was based on projections of intestinal EDTA concentrations and data from in vitro and rat studies with EDTA. However, the data from the 13-week dog study show an increased bioavailability (BA) of 2x at a 0.8x human EDTA dose equivalent. PK data from clinical studies with the 35 mg DR tablet (given 30 min before or immediately following breakfast) have shown a 2- to 3-fold increase in absorption (Ae) of RIS relative to the 35 mg IR tablet. Sponsor has argued that this increase is merely due to chelation of Ca in the food and increased availability of non-complexed soluble risedronate. However, under fasting conditions the BA of the DR formulation is also 44% higher than the IR tablet (Study 2007120), although this may be due to complexation of calcium in intestinal fluid. However, it can not be excluded that the increased risedronate absorption was at least in part due to an EDTA-induced increase in paracellular permeability and there is a potential for the DR tablet to increase the absorption of other paracellularly absorbed drugs. This issue is addressed by the Clinical Pharmacology Reviewer.

Conclusions

- **EDTA at doses used in the DR tablet may enhance risedronate absorption and risedronate-related systemic toxicities.**
- **EDTA at doses used in the DR tablet may exacerbate risedronate-related gastrointestinal toxicity.**
- **EDTA in the DR tablet may increase paracellular permeability to risedronate as well as co-administered drugs. This issue is addressed by the Clinical Pharmacology Reviewer.**

Discussion of EDTA toxicology

FDA has approved both disodium EDTA (Na_2EDTA) and disodium calcium EDTA ($Na_2CaEDTA$) as direct food additives (21 CFR 172) for use as preservatives, processing aids or color stabilizers, based on their metal chelation properties. EDTA came into widespread use as chelator in foods in the 1950's. EDTA has been tested in acute and chronic oral toxicity studies and in carcinogenicity, genotoxicity and reproductive toxicity studies. These studies were reviewed by JECFA/WHO (1974, 1993), Whittaker et al 1993 (CFSAN/FDA), Lanigan et al 2002 (CIREP) and/or

Heimbach et al (2000) in order to support the use of EDTA salts in foods and the use of Fe-EDTA salts as food iron fortificants.

EDTA is approved for the treatment of metal poisoning ($Na_2CaEDTA$) and the emergency treatment of hypercalcemia (Na_2EDTA) at high IV doses of up to 3 grams/day (50 mg/kg). It has also been used in 'chelation therapy' for non-approved indications with questionable safety at best. Adverse effects of high parenteral doses (g/day) include nephrotoxicity, cardiovascular effects (hypotension, other), dermatologic side effects, hypocalcemia (with Na_2EDTA), GI effects, hematologic, immunologic, muscle pain, headache, and possible teratogenicity. These side effects are unlikely to be an issue for an oral once-a-week product containing (b) (4) EDTA (b) (4)

<u>EDTA general toxicity</u>

EDTA is poorly absorbed from the GI tract in animals and humans. In humans and rats, 5-10% of an oral dose is absorbed and excreted unchanged by the kidney and most of the remainder is excreted unaltered in the feces within 1-3 days following dosing ($T_{1/2}$= 22 min in rats). In the GI tract the ions in the EDTA complex can freely exchange and different EDTA salts have been considered equivalent for safety evaluation. The oral LD_{50} of $CaNa_2EDTA$ is high at 0.4, 10, 7 and 12 g/kg in mouse, rat, rabbit and dog. The oral LD_{50} of Na_2EDTA in the rat is lower at 2 g/kg. Chronic toxicity studies have shown no adverse effects at dietary doses up to 250 mg/kg in rats and dogs. EDTA had no reproductive or developmental toxicity in rats when given orally with nutritionally (Zn) adequate diets. EDTA was negative in the Ames test and the mouse lymphoma assay and did not induce chromosome abnormalities in mammalian cell assays. EDTA was not carcinogenic in rats or mice. The data suggest that the weekly dose of (b) (4) Na_2EDTA is unlikely to cause adverse effects.

Effects of EDTA in oral toxicity studies

Species	Test compound	Study duration	Dose	Multiple of human (b) (4) dose (mg/m2 basis)	Effects	Refs
Rat	Na_2EDTA	90-day, (0, 0.5, 1, 5% of diet)	1% (1000 mg/kg) 5% (5000 mg/kg)	108x 540x	No effects Diarrhea, decrease in food consumption	Yang, 1952
Rat	Na_2EDTA	2-year	0, 0.5%, 5% (0, 500, 5000 mg/kg)	Up to 540x	No effects, including no effects on GI signs and bone ash content	Yang, 1952
Rat*	$CaNa_2EDTA$	2-year	0, 50, 125, 250 mg/kg/day (diet)	Up to 27x	No effects on survival, growth, clinical pathology, reproduction, tissue gross/histopathology (NOAEL 250 mg/kg/d)	(Oser et al 1963)* 4-generation study
Rat	Na_3EDTA	103 wks	0, 375, 750 mg/kg/day (diet)	Up to 80x	No survival effect, no signs of toxicity, no neoplastic or non-neoplastic lesions	NCI 1977
Mouse	Na_3EDTA	103 wks	0, 535, 1070 mg/kg/day (diet)	Up to 80x	No survival effect, no signs of toxicity, no neoplastic or non-neoplastic lesions	NCI 1977
Dog	$CaNa_2EDTA$	12-mo	0, 50, 100, 250	Up to 83x	No adverse findings (including selected	Oser et al

			mg/kg/day (diet)		tissue histopathology, bone radiography) (NOAEL 250 mg/kg/d)	1963
DOG	*Na_2EDTA*	*13 weeks*	*Oral capsule, fasted, 2.5, 12.5 mg/kg*	*0.8x, 4x*	*No adverse effects*	*NDA 22-560*

*ADI was derived from this study

ADI (Acceptable Daily Intake) of EDTA

The joint FAO/WHO Expert Committee on Food Additives (JECFA, 1974) established an ADI of EDTA of 2.5 mg/kg body weight, for disodium and Ca-disodium salts. This number was derived from a 2-year dietary study in FDRL rats with doses of 0, 100, 250 mg/kg $CaNa_2EDTA$ in which the NOAEL was 250 mg/kg (Oser et al, 1963). The NOAEL was divided by a safety factor of 100 to account for differences between animals and humans and variation between humans to yield an ADI of 2.5 mg/kg/day, equivalent to 150 mg/day. JECFA concluded that the use of $CaNa_2EDTA$ in foods is preferable to that of Na_2EDTA since the latter sequesters Ca more effectively. However Na_2EDTA may be used when needed. It was also stated that zink (Zn) nutritional status should be considered in relation to EDTA toxicity (e.g. teratogenicity) since EDTA effects may in effect be due to Zn deficiency. The ADI of 2.5 mg/kg/day was supported by the negative result of rat and mouse carcinogenicity studies (NCI, 1977). Subsequent committees and experts have reviewed the ADI of 150 mg/day and have found it adequate to protect human health. On a weekly basis, the ADI is 1050 mg/week.

EDI (Estimated Daily Intake) of EDTA

Overall exposure to EDTA from foods based on EDTA content of different foods (ppm) and daily food intake has been estimated at 15 mg/person/day or 0.25 mg/kg/day (Whitaker et al, 1993). This EDI was considered to be an upper bound and much higher than the daily intake estimated from known use of EDTA in the food supply (1.6 mg/day). The EDI of 0.25 mg/kg/day was refined to 0.13 mg/kg/day or 7.75 mg/day EDTA by Heimbach et al (2000). In addition, the 90th percentile daily intake of EDTA from the use of NaFeEDTA as fortificant in foods is estimated at 1.02 mg/kg/day (Heimbach et al 1999). Combined, the 90th percentile total EDI is 1.15 mg/kg/day, i.e., 75 mg EDTA per day, or 95 mg Na_2EDTA per day, which is below the ADI of 150 mg/day. The [redacted] (b) (4) Na_2EDTA dihydrate [redacted] (b) (4) mg Na_2EDTA) in the DR tablet will bring the maximum weekly dose to [redacted] (b) (4) (Na_2EDTA equivalents), which is still below the weekly ADI of 1050 mg.

EDTA effects on bone

EDTA had no effect on bone tissue (radiology, histology, ash content, strength) in animal studies in which diets had adequate mineral (Ca, Fe) content. However, in animal studies with relatively high parenteral doses (IV, IM), hypocalcemia and increases in PTH and bone turnover have been observed. The absence of bone effects in the 13-week dog study is consistent with the published data. Chelation therapy in humans with repeated IV infusions of 2-3 g EDTA/dose (20 infusion over 5-9 wks) has also been found to cause hypocalcemia, PTH increase and increases in bone resorption but not formation markers (Guldager et al, 1993) and the authors suggested that chelation therapy with EDTA is probably accompanied by bone loss.

The lack of an effect of EDTA on bone tissue in the referenced studies is probably due to the fact that absorbed EDTA is bound to and in equilibrium with serum Ca and will not enhance bone resorption unless the doses are very high and there is significant and sustained hypocalcemia that can not be compensated for by increased Ca absorption or decreased excretion. The data suggest that the (b) (4) Na_2EDTA dose in the DR tablet is unlikely to cause adverse bone effects.

Effects of EDTA on bone in nonclinical studies

Species	Test compound	Study duration	Route, Dose	Multiple of human (b) (4) g dose (mg/m2 basis) (assume 10% oral BA)	Effects	Refs
Rat	$CaNa_2EDTA$	2-year	Diet, 50, 125, 250 mg/kg	Up to 27x	No effect on tibia histology over 2 years; no changes in dental caries or bone calcification at 12 wks, no effect on tibia ash content at 2 years	Oser
Rat	Na_2EDTA	13 weeks	Diet, 1, 5, 10% (up to 10,000 mg/kg)	Up to 1080x	No histologic bone effects	Wynn
Rat	Na_2EDTA	90 days	Diet, 0, 0.5%, 1% (low Ca 0.54%, low Fe 0.013% diet)	54x, 108x	Dental erosion, decrease in bone ash content at 1% EDTA	Chan, 1956
Rat	Na_2EDTA	90 days	Diet, 0, 0.5%, 1% (normal mineral diet)	54x, 108x	No effects on dental erosion, bone ash content	Chan, 1956
Dog	$CaNa_2EDTA$	1-year	Diet, 50, 100, 250 mg/kg	Up to 83x	No changes in X-rays of chondrocostal junction, tibia and femur at all doses	Oser
Swine	EDTA	84 days	Diet, 289 ppm (14 mg/kg)	9x	No effects on metatarsal length, diameter, % ash, breaking strength	Owen
DOG	*Na_2EDTA*	*13 weeks*	*Oral capsule, fasted, 2.5, 12.5 mg/kg*	*0.8x, 4x*	*No effects on serum Ca or bone histology*	*NDA 22-560*
	Na_2EDAT + risedronate	*13 weeks*	*EDTA 2.5, 12.5 mg/kg RIS 8, 16 mg/kg*	*0.8x, 4x*	*No adverse effects on bone histology*	*NDA 22-560*
Dog	CaEDTA	1 month	IV, 150 uM/kg/day (44 mg/kg/d)	146x	No changes in histomorphometric parameters	Fukuda
Rat	EDTA	Single dose	IM, 100 mg/kg	108x	Hypocalcemia, PTH increase, osteocalcin increase	Thomas
Cow	Na_2EDTA	5h infusion	IV, 165 mg/kg	2200x	Hypocalcemia and hypophosphatemia; No significant effects on bone resorption markers OH-proline, DPD, ICTP	Liesegang

An interactive effect between EDTA and risedronate on the skeleton not evidenced by changes in calcium metabolism (e.g., increased Ca excretion), BMD (decrease) or bone turnover (increased resorption) is unlikely. The 13-week dog study with the risedronate-EDTA combination did not show adverse histological effects on bone. Bone hypertrophy

and decreased serum Ca and P were observed due to risedronate's anti-resorptive and hypocalcemic effects, respectively. Nonclinical bone quality studies to evaluate BMD, histomorphometry ,and biomechanics with the EDTA-risedronate combination were not requested for the NDA due to lack of concern.

Conclusions

- **Based on toxicology data with EDTA alone, the (b) (4) Na_2EDTA dose in the DR product is acceptable.**
- **The dose of (b) (4) Na_2EDTA in the DR risedronate tablet is unlikely to cause adverse effects including adverse effects on bone.**

Bone safety

In the pre-NDA meeting, the Division communicated a concern about the choice of the 35 mg dose with higher exposure than the approved 35 mg weekly tablet in the Phase 3 program. The Division mentioned a potential for altered calcium metabolism and impaired bone mineralization. Based on this concern it has been suggested that histomorphometry data from subjects treated with the 35 mg DR tablet are needed. These data will be collected after 2 years of treatment in Phase 3 Study 2007008 and have not yet been submitted.

In Clinical Study 2007008 with 5 mg IRBB, 35 mg DRBB and 35 mg DRFB groups, effects included increases in BMD (LS and proximal femur) and decreases in serum CTx, urine NTx, serum BAP that were slightly larger in the DR groups. There were no differences in serum Ca, P, Mg, or 24h urinary Ca excretion between treatment groups. An increased incidence of high iPTH levels and adverse events (AE) was observed in DR groups. PK data have shown a 2x-4x fold increase in urine Ae (amount excreted), probably reflecting increased absorption and systemic exposure, with the 35 mg DR compared to the IR tablet. The larger effects on BMD, bone markers, PTH and AE with the DR tablet may have been due to this increase in exposure.

This Reviewer does not believe that there is an increased risk for altered bone mineralization, i.e., osteomalacia or a mineralization deficit with the 35 mg DR formulation. Based on nonclinical data the safety margin for such an effect with risedronate is very high. All bisphosphonates (BP's) can inhibit mineralization at high doses (5-20 mg P/kg) which is probably a physicochemical effect. However, the potency to inhibit bone resorption varies greatly. Third generation amino-BP's such as risedronate, ibandronate and zoledronate potently inhibit bone resorption at doses far below those affecting mineralization (<1/1000x). Mineralization defects have only been observed with bisphosphonates such as etidronate for which the dose that inhibits mineralization is similar to the dose inhibiting bone resorption. Data from the Schenk assay with risedronate are included in the Actonel label and provide a large safety margin for mineralization impairment (800x). Support for the bone safety of risedronate also comes from bone quality studies in OVX rats and minipigs. These studies have shown suppression of bone turnover, increases in BMD and bone strength, maintenance of the BMD-strength relationship and no histological abnormalities at 4x-25x clinical dose multiples (Actonel® label, Section 13.2 Animal Toxicology and/or

Pharmacology). The data suggest that bone mineralization impairment or overt deterioration of bone quality is unlikely with the 35 mg DR tablet, even with a 2-4x increased exposure.

BMD data from Phase 3 Study 2007008 (5 mg IR vs. 35 mg DR) showed ΔLS-BMD @ 1 yr with 35 mg DR = 3.38 vs. 3.12 with 5 mg IR/day (1.08x). In this study exposure may have been up to 2x increased with the DR tablet. BMD data from Study HMR 4003E/3001 (5 mg IR daily vs 35 and 50 mg IR weekly) showed ΔLS-BMD = 4.12 with 50 mg IR/wk vs. 3.81 with 35 mg IR/wk (1.08x) and a 1.5 increase in AUC with 50 vs. 35 mg. These data are consistent and indicate similar exposure increase with the 50 mg IR compared to the 35 mg DR tablet. Histomorphometry data from Study HMR4003E/3001 showed the expected decrease in bone turnover (resorption, formation) but no differences between treatment groups in indices reflecting bone remodeling or bone formation such as Acf, MS/BS or BFR/BS or BFR/BV. Negative effects on bone mineralization or formation or evidence of oversuppression of bone turnover were not observed.

Atypical subtrochanteric femoral fractures have been observed in long term BP users. It has been suggested that these are due to 'oversuppression' of bone turnover and/or accompanying changes in the bone structural or material properties. The etiology of these fractures and their relationship to bisphosphonate use has not been elucidated. Long term studies in the intact dogs with alendronate have demonstrated bone changes that may be clinically relevant and could play a role in the generation of these fractures. However, the cause of these fractures in humans remains unclear and predictive biomarkers have not been identified. Since exposure appears to be increased with the 35 mg DR tablet and bisphosphonate-induced alterations in bone quality may occur that are exposure-related in the pertinent dose range, the DR product may be associated with an increased risk of potentially drug-related skeletal events such as atypical fractures.

Conclusions

- **Increased risedronate exposure with the DR product is unlikely to cause impairment of bone mineralization or deterioration of bone quality.**
- **Increased exposure with the DR product may lead to a higher risk for adverse events including potentially drug-related skeletal events.**

12 Appendices

APPENDIX 1 (Sponsor's Histopathology Tables)

Text Table 3
Incidence of Test Article-Related Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Males									
Liver									
Atrophy, Hepatocellular, Centrilobular									
Not Present	6	6	3	6	6	5	6	5	1
Minimal	0	0	2	0	0	1	0	1	3
Slight	0	0	1	0	0	0	0	0	2
Vacuolation, Hepatocytes, Centrilobular									
Not Present	6	6	4	6	6	6	6	6	5
Minimal	0	0	1	0	0	0	0	0	0
Slight	0	0	1	0	0	0	0	0	1
Decreased Glycogen									
Not Present	5	5	3	4	5	5	5	6	0
Present	1	1	3	2	1	1	1	0	6
Females									
Liver									
Atrophy, Hepatocellular, Centrilobular									
Not Present	6	5	4	6	6	4	6	4	2
Minimal	0	1	2	0	0	2	0	2	4

Text Table 4
Incidence of Test Article-Related Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Males									
Kidney									
Degeneration, Epithelium, Tubule									
Not Present	6	5	0	6	6	5	6	3	3
Minimal	0	1	4	0	0	1	0	3	2
Slight	0	0	2	0	0	0	0	0	1
Regeneration, Epithelium, Tubule									
Not Present	2	3	1	3	2	0	4	1	0
Minimal	4	3	1	3	4	5	2	4	2
Slight	0	0	4	0	0	1	0	1	3
Moderate	0	0	0	0	0	0	0	0	1
Inflammation, Chronic, Tubulointerstitial									
Not Present	6	6	3	5	5	2	6	5	2
Minimal	0	0	3	1	1	4	0	1	4
Enlarged Eosinophilic Tubular Epithelial Cells, Medulla									
Not Present	6	5	0	6	6	3	6	2	0
Minimal	0	1	3	0	0	2	0	4	3
Slight	0	0	3	0	0	1	0	0	3
Females									
Kidney									
Degeneration, Epithelium, Tubule									
Not Present	6	6	3	6	4	5	6	2	2
Minimal	0	0	3	0	2	0	0	4	1
Slight	0	0	0	0	0	1	0	0	3
Regeneration, Epithelium, Tubule									
Not Present	5	3	2	5	4	4	5	1	0
Minimal	1	3	3	1	1	0	1	2	2
Slight	0	0	1	0	1	1	0	3	1
Moderate	0	0	0	0	0	1	0	0	3
Inflammation, Chronic, Tubulointerstitial									
Not Present	6	3	3	3	5	2	6	2	1
Minimal	0	3	3	3	1	3	0	4	4
Slight	0	0	0	0	0	1	0	0	1
Enlarged Eosinophilic Tubular Epithelial Cells, Medulla									
Not Present	6	4	3	6	5	3	6	1	1
Minimal	0	2	3	0	1	1	0	5	0
Slight	0	0	0	0	0	2	0	0	5

Text Table 5
Incidence of Test Article-Related Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Males									
Stomach									
Mineralization, Epithelium									
Not Present	4	5	3	6	5	2	5	4	2
Minimal	2	1	1	0	1	1	1	1	2
Slight	0	0	2	0	0	0	0	1	1
Moderate	0	0	0	0	0	3	0	0	1
Single Cell Necrosis, Mucosa									
Not Present	6	0	0	6	2	1	6	2	2
Minimal	0	4	2	0	1	2	0	3	1
Slight	0	2	1	0	3	2	0	1	2
Moderate	0	0	3	0	0	1	0	0	1
Inflammation, Chronic, Mucosa									
Not Present	6	2	0	5	5	5	6	5	3
Minimal	0	4	4	0	0	0	0	1	2
Slight	0	0	2	1	1	1	0	0	1
Regenerative Hyperplasia, Gastric Pits									
Not Present	6	4	3	6	3	3	6	4	2
Minimal	0	1	1	0	2	3	0	2	3
Slight	0	1	2	0	1	0	0	0	1

Text Table 5 (Continued)
Incidence of Test Article-Related Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Females									
Stomach									
Mineralization, Epithelium									
Not Present	6	6	3	5	6	4	6	6	5
Minimal	0	0	1	1	0	1	0	0	1
Slight	0	0	1	0	0	1	0	0	0
Moderate	0	0	1	0	0	0	0	0	0
Single Cell Necrosis, Mucosa									
Not Present	6	5	2	6	5	3	6	1	2
Minimal	0	1	2	0	1	3	0	2	3
Slight	0	0	2	0	0	0	0	3	1
Inflammation, Chronic, Mucosa									
Not Present	6	5	3	6	5	4	6	3	4
Minimal	0	1	1	0	1	2	0	3	2
Slight	0	0	2	0	0	0	0	0	0
Regenerative Hyperplasia, Gastric Pits									
Not Present	6	6	3	6	6	2	6	2	3
Minimal	0	0	3	0	0	4	0	4	3

Text Table 6
Incidence of Test Article-Related Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Males									
Mesenteric Lymph Node									
Erythrocytes, Sinus									
Not Present	4	5	1	4	5	1	3	3	1
Minimal	2	1	1	2	1	2	3	1	0
Slight	0	0	3	0	0	3	0	2	1
Moderate	0	0	1	0	0	0	0	0	4
Females									
Mesenteric Lymph Node									
Erythrocytes, Sinus									
Not Present	6	6	1	5	5	3	6	2	3
Minimal	0	0	4	1	1	2	0	2	0
Slight	0	0	1	0	0	1	0	2	2
Moderate	0	0	0	0	0	0	0	0	1

Text Table 7
Incidence of Test Article-Related Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	0	0	2	0	0	1	0	0	2
Males									
Vein, Other									
Increased Prominence, Abdominal Vein									
Not Present	NA	NA	1	NA	NA	1	NA	NA	1
Minimal	NA	NA	0	NA	NA	0	NA	NA	1
Moderate	NA	NA	1	NA	NA	0	NA	NA	0
Females									
No. Examined	0	0	3	0	0	1	0	0	3
Vein, Other									
Increased Prominence, Abdominal Vein									
Not Present	NA	NA	0	NA	NA	0	NA	NA	2
Minimal	NA	NA	0	NA	NA	1	NA	NA	1
Slight	NA	NA	2	NA	NA	0	NA	NA	0
Moderate	NA	NA	1	NA	NA	0	NA	NA	0

NA = Not applicable.

Text Table 8
Incidence of Test Article-Related Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Males									
Testis									
Hypospermatogenesis									
Not Present	2	6	2	3	1	2	5	5	2
Minimal	3	0	3	2	4	3	1	0	0
Slight	0	0	1	1	1	0	0	0	4
Moderate	1	0	0	0	0	1	0	1	0
Multinucleated Giant Cells									
Not Present	4	5	4	3	6	5	5	3	1
Minimal	2	1	2	3	0	1	1	2	3
Slight	0	0	0	0	0	0	0	1	1
Moderate	0	0	0	0	0	0	0	0	1

Text Table 9
Incidence of Selected Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Males									
Heart/Ascending Aorta									
Mineralization, Ascending Aorta									
Not Present	5	6	3	6	4	5	6	4	4
Minimal	1	0	0	0	2	0	0	0	1
Slight	0	0	3	0	0	1	0	2	1
Females									
Heart									
Mineralization, Ascending Aorta									
Not Present	6	6	4	6	6	4	5	3	5
Minimal	0	0	0	0	0	0	1	1	1
Slight	0	0	2	0	0	2	0	2	0

Text Table 10
Incidence of Expected Pharmacologic Microscopic Findings

NE-58095 mg/kg/dose:	0	8	16	0	8	16	0	8	16
EDTA mg/kg/dose:	0	0	0	2.5	2.5	2.5	12.5	12.5	12.5
No. Examined:	6	6	6	6	6	6	6	6	6
Males									
Rib									
Primary Spongiosa Persistence/Hypertrophy									
Not Present	6	0	0	6	0	0	6	0	0
Slight	0	4	4	0	5	3	0	1	1
Moderate	0	2	2	0	1	3	0	5	5
Sternum									
Primary Spongiosa Persistence/Hypertrophy									
Not Present	6	0	0	6	0	0	6	0	0
Slight	0	6	6	0	6	6	0	6	6
Nasal Turbinates									
Increased Bone									
Not Present	6	2	0	6	3	1	6	1	0
Minimal	0	4	2	0	2	3	0	3	2
Slight	0	0	4	0	1	2	0	2	4
Females									
No. Examined:	6	6	6	6	6	5	6	6	6
Rib									
Primary Spongiosa Persistence/Hypertrophy									
Not Present	6	0	0	6	0	0	6	0	0
Slight	0	5	4	0	4	2	0	3	2
Moderate	0	1	2	0	2	3	0	3	4
Sternum									
Primary Spongiosa Persistence/Hypertrophy									
Not Present	6	0	0	6	0	0	6	0	0
Slight	0	6	6	0	6	5	0	6	6
No. Examined:	6	6	6	6	6	6	6	6	6
Nasal Turbinates									
Increased Bone									
Not Present	6	2	3	5	2	0	6	3	1
Minimal	0	4	2	1	4	5	0	2	3
Slight	0	0	1	0	0	1	0	1	2

APPENDIX II

Toxicity studies in dog

Dose regimen	Doses	NOAEL	LOAEL	Toxicities at LOAEL	Cmax (ng/mL) (total drug) at NOAEL	AUC (ngxh/mL) (total drug) at NOAEL
DAILY						
13-wk (B8)	0, 0.5, 2, 4, 8	4	8	Liver atrophy, increased liver enzymes, renal cortical cell necrosis, testicular lesions, spermatid arrest	nd	nd
13-wk (B9)	0,6,8,12	6	8	Testicular degeneration, oligospermia, serum chemistry changes (liver enz)	295	620
1-year (B18)	0, 4, 8, 16, 32	4	8	Mortality (females), clinical signs, kidney and brain weight increase, toxicity in liver (increased AST, CK, bile acids, hepatocyte degeneration, atrophy), stomach (gastropathy, edema, erosion), intestine (hemorrhage, congestion), kidney (nephropathy, hemorrhage, necrosis), testes (degeneration), esophagus (erosion), pancreas (edema, inflammation), lymph node (atrophy, hemorrhage)	196	624
		8	16,32	Mortality (m and f)	483	1893
2-year (B17, B19)	0, 0.2, 0.5, 2 (daily) 0.5, 2, 8 for 7 days, then 21 days placebo	>>2	>2	No toxicities	nd	nd
MONTHLY						
6-month (old)	0, 16, 32, 64	<16	16	Stomach (necrosis, regeneration, inflammation), esophagus (inflammation, erosion, hyperplasia)	<2090	<7558
		16	32	GI clinical signs, liver (increased AST, ALT, ALP, bile acid, atrophy, bile duct hyperplasia, glycogen decrease, pigment), kidney (inflammation, tubule degeneration enlarged tubule cells)	2090	7558
1-year (young)	0, 16, 32, 64	<16	16	Stomach (regeneration, inflammation, erosion, *females*), kidney (tubule degeneration, *males*), bone (hypertrophy primary spongiosa)	<1988	<6683
		16	32	Stomach (regeneration, inflammation, erosion, *males*), kidney (tubule degeneration, inflammation, *males and females*), liver (AST, ALT, bile acid increase, atrophy, bile duct changes, sinusoid pigment)	1988	6683
		32	64	Mortality	5423	25817

Nd= not determined

APPENDIX III

Label - Nonclinical Sections

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22560	ORIG-1	WARNER CHILCOTT CO LLC	(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEMMA A KUIJPERS
05/13/2010

LYNNDA L REID
05/14/2010
I concur with recommendations of the primary reviewer, Dr. Kuijpers: nonclinical data support approval and recommended labeling is acceptable.

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY
45-DAY FILING MEMO

NDA:	NDA 22-560 (Original NDA)
Applicant:	Procter & Gamble Pharmaceuticals (b) (4)
Drug Name:	(b) (4) (Risedronate sodium delayed-release)
Route, formulation:	Oral, Tablet
Regimen:	Once weekly
Active ingredient:	35 mg anhydrous risedronate sodium
Inactive ingredient:	EDTA (b) (4) compendial
Indication(s):	(b) (4) Treatment of postmenopausal osteoporosis (b) (4)
Letter Date:	September 24, 2009
60-Day Filing Date:	November 23, 2009
74-Day Letter Date:	December 7, 2009
PDUFA Goal Date	July 24, 2010 (standard) March 24, 2010 (priority)
IND:	74,086
Project Manager:	Karl Stiller
Memo date:	November 3, 2009

BACKGROUND

NDA 22-560 for (b) (4) is for a novel once-a-week risedronate delayed-release (RIS-DR) tablet formulation (35 mg) that allows for dose administration in the morning with (b) (4) food. (b) (4)

The currently marketed ACTONEL® immediate release (IR) product labeling requires that the product should be taken "at least 30 minutes before the first food or drink of the day other than water" because of risedronate's significant food effect due to formation of insoluble complexes with divalent and trivalent metal ions, which decreases its absorption and bioavailability.

The RIS-DR formulation was developed based on the premise that absorption of RIS in presence of food may be improved if it was delivered at sites beyond the stomach (b) (4) The novel enteric coated RIS-DR tablet has a pH trigger of 5.5 and contains a chelator (EDTA) (b) (4)

(b) (4).

The sponsor proposes to continue the use of the "30 minute wait to lie down" statement employed in the current ACTONEL label and reduce the requirement for water intake with the tablet from 6-8 to 4 ounces.

Risedronate NDA submissions

NDA Submission	Date	Action	Product	Dose/form	Indication
20-835 original	March 31, 1997	AP March 27, 1998	Risedronate (Actonel)	Daily, 5 mg	Paget's disease
20-835/S001	Dec 18, 1998	April 14, 2000	Risedronate (Actonel)	Daily, 5 mg	Treatment of corticosteroid-induced osteoporosis
20-835/S002	Dec 18, 1998	April 14, 2000	Risedronate (Actonel)	Daily, 5 mg	Treatment of postmenopausal osteoporosis
20-835/S003	Dec 18, 1998	April 14, 2000	Risedronate (Actonel)	Daily, 5 mg	Prevention of postmenopausal osteoporosis
20-835/S004	Dec 18, 1998	April 14, 2000	Risedronate (Actonel)	Daily, 5 mg	Prevention of corticosteroid-induced osteoporosis
20-835/S008, S009	July 23, 2001	May 17, 2002	Risedronate (Actonel)	Once weekly. 35 mg	Treatment and prevention of postmenopausal osteoporosis
20-835/S023	Oct 20, 2005	Aug 11, 2006	Risedronate (Actonel)	Once weekly. 35 mg	Treatment of osteoporosis in men
20-835/S025	June 15, 2006	April 16, 2007	Risedronate (Actonel)	Once monthly, 75 mg on two consecutive days	Prevention and treatment of postmenopausal osteoporosis
20-835/S030	Oct 11, 2008	April 22, 2008	Risedronate (Actonel)	Once monthly 150 mg	Treatment of postmenopausal osteoporosis
21-823	August 30, 2004	August 12, 2005	Risedronate plus calcium (Actonel Plus Calcium	Weekly, 35 mg tablet plus 1250 mg calcium carbonate tablet	Prevention and treatment of postmenopausal osteoporosis
22-560	Sept 24, 2009	N/A	Risedronate	Weekly, 35 mg, tablet delayed-release formulation (RIS-DR), with (b) (4) EDTA	Treatment (b) (4) of postmenopausal osteoporosis (b) (4)

REGULATORY

IND 74,086 for the delayed release formulation was submitted to DMEP on June 13, 2006. A pre-IND meeting was held February 15, 2006. At the pre-IND meeting it was communicated to the sponsor that additional nonclinical safety data are not required for EDTA (edetate disodium) at planned weekly doses of (b) (4) In another communication to the sponsor (May 26, 2006), the Division noted that EDTA would be categorized as excipient and would not be considered an active ingredient.

After a Phase II study was completed, and EOP2/pre-Phase III meeting was held with DMEP on 28 June, 2007 to discuss the Phase III program and the NDA requirements. A pre-NDA meeting was held with DRUP on 21 April 2009.

The NDA includes 2 early concept clinical studies and nine clinical studies to support approval of the NDA (7 Phase 1 studies, 1 Phase II efficacy/safety/PK study) and 1 Phase III (efficacy/safety study, Study #2007008), and 2 in vitro studies and 1 population PK/PD modeling study.

CMC

Quantitative Composition - Risedronate Sodium Delayed-Release Tablets, 35 mg

Ingredient	Function	Unit Quantity (mg/tablet)	% w/w
(b) (4)			
Risedronate sodium	Active	35.0 a, b	10.00
ProSolv SMCC 90	(b) (4)		
Edetate disodium, c USP			
Sodium starch glycolate, NF			
Stearic acid, NF			
Magnesium stearate, NF			
(b) (4)			
(b) (4)			
Methacrylic acid copolymer (b) (4) NF (b) (4)			
(b) (4)			
Triethyl citrate, NF			
Talc, USP			
Ferric oxide, NF, yellow			
Simethicone, USP			
Polysorbate 80, NF			
(b) (4)			
Target Total Enteric Coated Tablet Weight		350 mg	100.0

a Equivalent to 32.48 mg risedronic acid.
b (b) (4)
c Edetate disodium, USP. (b) (4)
d (b) (4)
e (b) (4)
(b) (4)
f

The EDTA content of the DR tablet formulation is (b) (4). On a cumulative basis, a dose of (b) (4) is lower than the maximum acceptable daily intake (ADI) of 2.5 mg/kg/day $CaNa_2$-EDTA (equivalent to 149 mg/day Na_2EDTA dehydrate, for a 60 kg person) recommended by Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1973. The current estimated daily mean intake of EDTA is (b) (4), which is well below the ADI of 150 mg/day. Thus, the weekly dose of (b) (4) in the

risedronate-EDTA combination formulation was considered acceptable for the clinical studies conducted to support this NDA.

NONCLINICAL

A complete pharmacology/toxicology development program was conducted with risedronate to support NDA 20-835. Toxicity studies were conducted in rats and dogs mostly by oral dosing. Target organs included liver, kidney, stomach, testes, lung, pancreas, lymph nodes. Reproductive toxicity was observed in rats. Data from carcinogenicity studies in rats and mice were submitted to NDA 20-835/S-001/S002 (b) (4) and were negative.

Pharmacology and Pharmacokinetics

There were no new nonclinical pharmacology or in vivo pharmacokinetic studies to support the NDA. In Module 2.6 (Nonclinical Written and Tabulated Summaries) pharmacology and pharmacokinetic study summaries were not included. All nonclinical pharmacology and in vivo pharmacokinetic studies were submitted to NDA 20-835. Reviewer will refer to the nonclinical data submitted to NDA 20-83 to address nonclinical pharmacology of pharmacokinetics issues.

Two in-vitro study reports entitled "Effects of EDTA on the Solubility of Narrow Therapeutic Index Drug Products and Antivirals", and "Potential Interaction of Delayed-Release Actonel® Tablets with Divalent and Trivalent Cations in Other Co-administered Medications" were included in Section 4 (Nonclinical Study Reports) under 4.2.2 (Pharmacokinetics), under 4.2.2.6 'Pharmacokinetic Drug Interactions'. Discussion of these reports is located in Section 2.7.2. (Summary of Clinical Pharmacology Studies) under 2.7.2.1 (Background an Overview)

Toxicology

In the review of the original submission of IND 74,086, the P/T Reviewer recommended that the sponsor consider conducting an exploratory animal toxicity study with a risedronate-EDTA combination to identify potential changes in GI effects as compared to those caused by risedronate alone (Review July 14, 2006).

At the EOP2 meeting on June 28, 2007, for IND 74,806, information on gastrointestinal toxicity from a nonclinical study with risedronate in combination with EDTA was requested by the Division (DMEP). The purpose of the study was to determine the gastric and lower GI toxicity and TK of risedronate in the presence of EDTA. The sponsor submitted a study protocol (b) (4) but this protocol was not considered adequate. An amended protocol with two fixed doses of EDTA was subsequently submitted and considered adequate. Dogs were dosed via oral capsule, weekly for ≥ 13 weeks, with a combination of NE58095 (risedronate sodium) (0, 8, 16 mg/kg/wk) and EDTA (0, 2.5, 12.5 mg/kg/wk). Bone tissue was examined by histology only. The study report was included in the current NDA submission. The data from this 13-week dog study can be used to bridge to other previously submitted toxicity data, e.g.

chronic toxicity studies. The data are relevant to support the safety of the new clinical formulation.

Bone quality/toxicity

Nonclinical bone quality studies with daily oral doses of risedronate have previously been conducted in rats and minipigs. The data are included in the animal pharmacology section of the label (Section 13.2). The highest doses used in these studies were equivalent, on mg/m2 basis, to 4x and 25x the human 5 mg daily dose, respectively (based on mg/m2 comparison). The data from both species support the relationship between bone mass (BMD) and strength. The label also mentions that in the Schenk rat assay risedronate did not interfere with bone mineralization even at the highest dose tested, which was approximately 800 times the human daily dose of 5 mg (based on mg/m2 comparison).

The issue of bone quality is potentially of concern for the DR formulation since systemic exposure to risedronate is higher with the DR than with the IR tablet formulation and because bone will be exposed once-weekly to (b) (4) chelator EDTA in combination with risedronate, although the dose of EDTA is relatively low (<ADI of 149 mg/day). Potential bone toxicity of the DR tablet needs to be addressed in the nonclinical and clinical NDA reviews. Clinical histomorphometry data have been submitted to address this concern.

Labeling

The proposed labeling contains nonclinical findings in Section 8 (Use in Specific Populations - Pregnancy, Nursing Mothers), Section 12 (Clinical Pharmacology) and Section 13 (b) (4)

From the Pharmacology/Toxicology perspective, this NDA can be filed.

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		

2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission, communications/discussions, completed and submitted in this NDA?	X		Yes. A report of a nonclinical 13 week dog toxicity study requested to provide data on the GI effects of risedronate plus EDTA was submitted with the NDA.
Have electronic files of the carcinogenicity studies been submitted for statistical review?	N/A		
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie.,	X		

adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?			
7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	X		
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	X		
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:	N/A		

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22560	ORIG-1	PROCTER AND GAMBLE PHARMACEUTICALS INC	(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

GEMMA A KUIJPERS
11/03/2009

LYNNDA L REID
11/09/2009